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FETAL AND NEONATAL EDITION

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FETAL AND NEONATAL EDITION

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Annotations

Herpes simplex virus infection in pregnancy

The incidence of neonatal herpes simplex virus (HSV) infection is about 200–500 per 100 000 live births in the USA[1 2] but has been estimated at two per 100 000 in the UK.[3] Neonatal HSV results from perinatal acquisition from the maternal genital tract in about 85% of cases. Approximately 5% of cases result from transplacental spread resulting in intrauterine HSV,[4] while about 10% of cases are secondary to postnatal acquisition.[5]

Intrauterine HSV infection

Nine (4·7%) of 192 infants with neonatal HSV infection enrolled in a large prospective US study had evidence of intrauterine HSV infection.[4] These nine babies, and four other babies selectively referred to the authors, had a combination of skin lesions and scars at birth, chorioretinitis, microcephaly or hydranencephaly, and microphthalmia. Eight mothers were asymptomatic, four had apparent primary genital HSV infection (two in the first and two in the third trimester), and one mother had recurrent genital herpes. The risk of intrauterine infection if the mother has proved primary genital herpes in pregnancy is unknown, but is probably very small.[6]

Maternal HSV infection

About 70% of babies with neonatal HSV infection are born to mothers with no history of genital lesions.[5] Most neonatal cases result from primary maternal HSV infection around the time of delivery, as determined by IgM production, although the maternal infection may be asymptomatic.[1] Of those asymptomatic women who have HSV detected in early labour, about a third have primary genital infection, and their babies are 10 times more likely to develop neonatal HSV than babies of women with asymptomatic reactivation. A distinction has been drawn between women with *primary* genital herpes, who become infected with either HSV-1 or HSV-2 in the absence of prior HSV antibodies, and those with so called *non-primary* infection, who have a first symptomatic genital infection, usually with HSV-2, in the presence of neutralising HSV IgG antibodies, usually to HSV-1. For the USA it has been estimated that the relative proportions of recurrent, primary, and non-primary HSV infections at the time of labour are 91·3%, 2·1%, and 6·6% respectively.[7] It was originally thought that non-primary maternal infections were less likely to lead to neonatal infection.[6] However, in a recent study of babies born vaginally to asymptomatic women who were found by viral culture to be shedding HSV at delivery, infection developed in two of five babies of mothers with primary infection and four of 13 with non-primary infection,[1] suggesting that anti-HSV-1 antibody may not be as protective against HSV-2 infection as once thought.

Specific maternal IgG antibody against the relevant HSV serotype protects against neonatal infection, but this protection is not absolute. Prober *et al*[8] and Brown *et al*[1] studied babies born vaginally to women with recurrent HSV infection who were shedding virus at the time of delivery. In the study of Prober *et al* none of 34 exposed babies became infected, and their neutralising antibody levels to HSV type 2 were significantly higher than those of historically infected babies. In the study of Brown *et al*, one of 33 exposed babies became infected. Thus neonatal HSV infection may follow recurrent maternal HSV infection, although it is more common following primary (and non-primary) infection.

Neonatal infection

Neonatal HSV infection may be *localised* to skin, eye or mouth, may be *generalised* to involve the liver, adrenals, lungs, and other organs including the brain, may cause isolated *pneumonitis*, or there may be isolated *meningoencephalitis*. The prognosis of all but the first form is poor. Without antiviral treatment about 70% of babies with localised HSV infection will progress to disseminated infection.[9] With increasing recent recognition that neonatal vesicular skin eruptions are often herpetic, specific diagnosis by immunofluorescent staining or electron microscopy and early antiviral treatment, there has been a marked fall in the proportion of cases of neonatal HSV infection in the USA that are disseminated, and a concomitant increase in the proportion of babies with localised disease.[10]

The two drugs that have been shown to be effective in neonatal HSV infection are acyclovir and adenosine arabinoside (ara-A), and the two drugs are almost identical in terms of mortality and long term morbidity.[11] Even with these drugs, however, the mortality of disseminated disease is 50–60%.[11]

There is considerable concern that neonatal HSV infection may cause chronic, insidious central nervous system infection leading to progressive neurodevelopmental deterioration. Gutman *et al* described babies with neonatal HSV encephalitis who deteriorated after completing antiviral treatment or had progressive deterioration over their first year of life.[12] Even more alarmingly, Whitley *et al* found that four of 71 babies with neonatal HSV infection localised to the skin, eyes, or mouth had long term neurological damage.[13] All four babies had HSV-2 and had three or more recurrences of

Management of HSV infection in pregnancy

Maternal infection	*Risk to fetus/baby*	*Management of mother*	*Management of baby*
Primary in 1st trimester	≤20% of abortion or intrauterine infection	No action	As for recurrent herpes
First ever lesions at delivery			
(a) Primary	About 50% risk of neonatal HSV[6]	Caesarean section	†Cultures if caesarean section performed treat with acyclovir if positive. Prophylactic acyclovir if delivers vaginally
(b) Recurrence	Unknown	Vaginal delivery	†Cultures treat with acyclovir if positive
(c) Unknown	About 30% chance infection is primary	Caesarean section	†Cultures: treat with acyclovir if positive
Recurrent genital herpes, no signs or symptoms	≤3% of neonatal HSV[1 8]	Vaginal delivery	Observe for signs *or* †cultures and treat with acyclovir if positive

†Cultures=nasopharyngeal+conjunctival viral culture at 24–48 hours of age

skin vesicles in the first year of life. Strong consideration should be given to long term oral acyclovir prophylaxis, perhaps for a year, for all babies with neonatal HSV encephalitis and for babies with localised HSV-2 infection who have three or more skin recurrences.

Prevention of neonatal HSV infection

The risk to the fetus of stillbirth or intrauterine infection when the mother has primary genital herpes in the first trimester is unknown, but probably small.[6] Acyclovir treatment of the mother under these circumstances has not been evaluated. Acyclovir appears to cross the placenta only in small quantities,[14] and its safety for the fetus is unproved, so its use does not seem indicated.

The transmission rate to babies at highest risk, those whose mothers have active, primary genital herpes at delivery, is about 50% if they are delivered vaginally.[6] Caesarean section, particularly if performed within 24 hours of membrane rupture, reduces the risk of neonatal HSV infection,[15] although some babies, perhaps 15–20%, will still be infected.

In clinical practice, it is not always clear whether a woman presenting with her first episode of clinical genital herpes infection at delivery has primary or recurrent disease. About 30% of such women will have primary infection.[1] If there is not sufficient time to determine whether the mother has specific IgM, then it seems wise to advise caesarean section.

The risk to a baby of an asymptomatic woman with a history of recurrent genital herpes is low.[1 8] The baby should be delivered vaginally. When a mother with recurrent genital herpes has active genital lesions at term, either symptomatic or on cervical examination, the risk to the baby is probably higher than if she is asymptomatic since the baby is likely to receive a greater viral load. Some authorities would advise caesarean section, although we feel that a more conservative approach is acceptable (see table). At present there are insufficient data on safety to advise giving acyclovir to pregnant women with HSV infection.

At one stage it was widely advocated that women with a history of recurrent genital herpes should have screening cervical viral cultures taken near term, but this would prevent very few cases of neonatal herpes In the USA it would cost $1·9 million per case averted and there would be one maternal death from complications of caesarean section for every 10 neonatal cases prevented.[16] Rapid antigen detection for HSV in genital specimens at delivery would identify most at-risk babies, but result in a large number of caesarean sections. Libman *et al* have analysed different strategies for prevention of neonatal HSV infection, and concluded that maternal physical examination at onset of labour would give the best results in terms of numbers of cases of neonatal HSV averted for least number of extra caesarean sections.[7]

There is no clear consensus as to the management of asymptomatic babies born to women with genital herpes under the different circumstances described above. The alternatives are that the baby should be treated with acyclovir from birth, should have nasopharyngeal and conjunctival viral cultures taken at 24–48 hours of age (indicating true colonisation rather than surface colonisation), and be treated with acyclovir only if positive, or should simply be observed and treated if symptomatic.[17] Evidently the greater the risk of neonatal HSV developing, the more reasonable it is to use aggressive intervention. Possible strategies are outlined in the table. Any at-risk baby with signs suggestive of neonatal HSV infection should be treated with acyclovir or ara-A until the baby's infection status is clarified.

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Kidney function in the very low birthweight infant

In recent years there have been considerable advances in understanding the mechanisms of how the kidney grows and develops, which have shed light on the aetiology of some renal malformations and physiology.[1] During fetal life the excretory role of the kidney is minimal and even the anephric fetus enjoys biochemical homoeostasis. Fetal urine production begins at about 10 weeks of gestation increasing progressively to 28 ml/hour at term. Birth immediately imposes an excretory and fluid conservatory role on the neonatal kidney. The term baby is well adapted for the demands of postnatal life. In contrast the very low birthweight (VLBW) baby's renal function is more immature and the maintenance of normal fluid and electrolyte balance is difficult. Significant hyponatraemia (serum sodium concentration less than 130 mmol/l) occurs in up to 43% of babies less than 30 weeks' gestational age.[2] The difficulties of maintaining electrolyte homoeostasis are further compounded because the volume of distribution of sodium changes with extracellular fluid volume decreasing from 62% at 16 weeks to 43% at term.[3] The VLBW infant is, therefore, in a state of relative overhydration. In the sick VLBW infant with asphyxia, sepsis, intracranial haemorrhage, pulmonary disease or renal failure, high circulating concentrations of antidiuretic hormone and atrial natriuretic factor make electrolyte requirements more unpredictable. A better understanding of the renal function of the VLBW infant is needed if appropriate management strategies are to be developed and the series of papers by Barry Wilkins in this edition of the journal sheds further light on some aspects of their renal adaptation.[4–7]

Nephrogenesis proceeds under a complex series of controls and is complete at 36 weeks' gestation with the full compliment of 1 million nephrons. After birth glomerular filtration rate increases in a preordained way from a mean of 0·6 ml/minute at 26 to 1·4 ml/minute at 33 weeks' postconceptional age. Uncomplicated respiratory distress syndrome does not affect this maturation. Plasma creatinine concentration, which is generally used as a simple measure of glomerular filtration rate, is of limited value in the VLBW infant because of the wide normal ranges and the presence in the plasma of substances which interfere with its measurement. In these studies Dr Wilkins has measured true plasma creatinine but even so the normal ranges are wide, making the diagnosis of renal insufficiency difficult.

Hyponatraemia is a common problem in VLBW infants.[8] Theoretically it may result from excessive sodium loss, water retention, or redistribution of sodium within body fluid spaces. Its management is controversial: some suggesting water restriction, others sodium supplementation. Correct management requires knowledge of the plasma and urine urea, creatinine, electrolytes, their volumes of distribution in body fluid spaces, and urine flow rates and these studies provide information about them. Timed urine collections are difficult to obtain and the formula derived by Wilkins: urine flow rate, $V=90{\cdot}5/\text{urine creatinine}$ (μmol/l) could prove useful to tailor urine, water and electrolyte losses, although information based upon single urine samples must be interpreted with caution because of the large fluctuation in urine flow rates observed in these babies. Using this formula a wide range of urinary sodium losses up to 21 mmol/kg/day was observed, lending support to those who recommend sodium supplementation. However, VLBW infants are in a state of relative hypervolaemia and the increased urinary losses may be physiological.[3] Measurement of the extracellular fluid and circulatory blood volumes would help to resolve this dilemma, but there is no simple reliable technique to do so. Body weight changes are imprecise in ventilated babies with intravenous catheters and infusion lines. High plasma urea concentrations are not helpful either as they may reflect increased catabolism rather than dehydration.

There is still much we do not understand about the renal function of the VLBW baby. A better understanding of the physiological changes is needed to improve the management of the fluid and electrolyte problems they present. This series of papers by Wilkins provides some helpful observations that will be useful to tailor the fluid and electrolyte management of individual babies to their requirements.

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ORIGINAL ARTICLES

Renal function in sick very low birthweight infants: 1. Glomerular filtration rate

Barry H Wilkins

Abstract

A total of 135 measurements of polyfructoside clearance as a measure of glomerular filtration rate (GFR) were made in 39 infants of 25·5–33 weeks' gestation, birth weight 720–2000 g, between the ages of 0·5 and 33 days. GFR was related to postconceptional age and increased exponentially from geometric mean 0·59 ml/min at 26 weeks' postconceptional age to 1·40 ml/min at 33 weeks. GFR in the first week and GFR at later ages were the same for a given postconceptional age. GFR was the same in sick infants with severe ventilatory failure as in less ill infants. There was no evidence that GFR was influenced by nitrogen input. GFR increases postnatally in a preprogrammed way irrespective of other postnatal events. When factored by body weight GFR in the first week increased only little from arithmetic mean 0·70 ml/min/kg at 26 weeks to 0·84 ml/min/kg at 33 weeks, but older infants often had a falsely high GFR per kg when they lost weight in the first week or two after birth or failed to gain weight later.

(*Arch Dis Child* 1992,67:1140–5)

There have been many but conflicting reports concerning the maturation of glomerular filtration rate (GFR) in preterm infants.[1–10] Most emphasise that GFR is low compared with that in older children, and that this limits excretory ability, and that there is a rapid postnatal increase. Measurement of GFR and other aspects of renal function is more difficult in the smallest infants especially in the first week when they may be oedematous and ill and because of inherent difficulties with urine collection, and much of the discrepancy between studies may reflect experimental differences. Careful studies have shown that GFR increases after birth slowly and progressively in a preprogrammed way dependent only on postconceptional age in well preterm infants.[1 2] Few studies have examined GFR in the sickest and most immature infants.

The purpose of the present study was to refine existing methods of measuring GFR by polyfructoside clearance and to examine postnatal changes in GFR in very low birthweight infants including some with severe respiratory disease. The study had health authority ethical committee approval and informed parental consent was obtained.

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Patients and methods

This study was part of a wider study of renal glomerular and tubular function in 42 very low birthweight infants, chosen to be studied in the first postnatal week, and later if possible. Gestation at birth was 25·5–33 weeks, birth weight 720–2000 g. Two infants were over 1500 g. The exact timing of the studies was difficult because so many different events befell the patients that it was impossible to perform clearance studies at the same age and on the same number of occasions in all subjects and clearance studies were only performed when intravenous treatment was being given. The polyfructoside used was Polyfructosan-S (Laevosan-Gesellschaft), an inulin substitute hereafter called PF-S. Many experiments failed and were irretrievable because of interruption of the PF-S infusion or acute clinical deterioration requiring resuscitation or administration of plasma. Some subjects received various drugs occasionally (for example frusemide, aminophylline boluses, indomethacin, digoxin, and vancomycin) or plasma for volume replacement that might interfere with results, so they were not studied for 24–48 hours afterwards. Most did receive aminophylline, which is routinely used as a respiratory stimulant, being commenced between age 2 and 14 days. The author has found no evidence of significant renal effect of chronic aminophylline administration.[11]

All patients were managed clinically by neonatal physicians. Water treatment was started according to the regimen: 60, 90, 120, 150, 150, etc ml/kg/day (days 1, 2, 3, 4, ≥5) for infants >1500 g; 80, 120, 150, 180, 180, etc for 1000–1500 g; and 100, 130, 150, 180, 200, etc for <1000 g. Sodium was started at 3, 4, and 5 mmol/kg/day in these three weight groups from the second day. There was complete freedom to vary these regimens according to individual circumstances. Extra sodium was only given in response to evidence of sodium depletion with hyponatraemia and high urine sodium losses. This was common after the middle of the second week. Potassium was given from the second day at 1–2 mmol/kg/day and was rarely varied. Glucose was started at 6–8 mg/kg/min (as 10% glucose) and changed according to blood glucose concentration. Nitrogen was given as Vamin 9 glucose (KabiVitrum) 40 ml/kg/day (380 mg nitrogen/kg/day) from the third day when tolerated. Actual water, sodium, potassium, and nitrogen inputs are summarised in the table. One baby had prenatal steroid.

Mean, minimum, and maximum water, sodium, potassium, and nitrogen inputs for all infants in the two age periods 3–10 days and 11–21 days

	3–10 days	*11–21 days*
Sodium (mmol/kg/day)		
Mean (min, max)	4 7 (1 2, 9 7)	6 2 (1 2, 12 3*)
Potassium(mmol/kg/day)		
Mean (min, max)	1 6 (0, 3·5)	1·9 (0, 4 2)
Water (ml/kg/day)		
Mean (min, max)	152 (77, 233)	154 (84, 222)
Nitrogen (mg/kg/day)		
Mean (min, max)	230 (0, 476)	218 (0, 560)

*One infant who was severely sodium depleted received 18 mmol/kg sodium on day 21

The infants were evenly distributed about the 50th weight centile according to the growth charts of Keen and Pearse.[12] Four subjects never lost weight after birth, one less than and three greater than 28 weeks' gestation. Three of these developed patent ductus arteriosus (PDA) at 3 to 7 days of age when their weights had increased by 2%, 5%, and 8%. A further two gained weight initially before eventually losing weight. These two also developed PDA at 2 and 6 days with weights equal to and 4% above birth weights. All the other subjects lost weight after birth, reaching a nadir at 3 to 10 days when weight was 3% to 23% below birth weight. Twelve of these developed PDA at 2 to 8 days when weight was up to 23% below birth weight. In eight of these 12 the PDA developed when the weight was more than 10% below birth weight. In the subjects who lost weight, birth weight was regained at age 10 to 31 days (median 17). In those less than 28 weeks' gestation the median was 24 days and in those greater than 28 weeks 13·5 days.

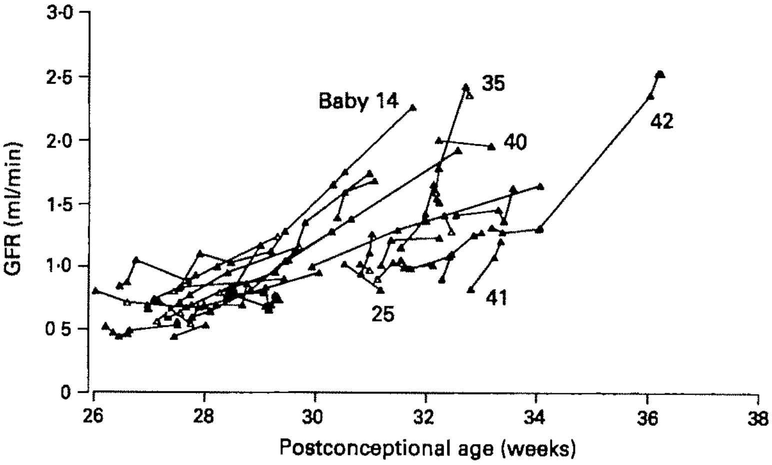

Figure 1 GFR uncorrected for body size as a function of postconceptional age (n=135). Sequential points are joined for individual subjects.

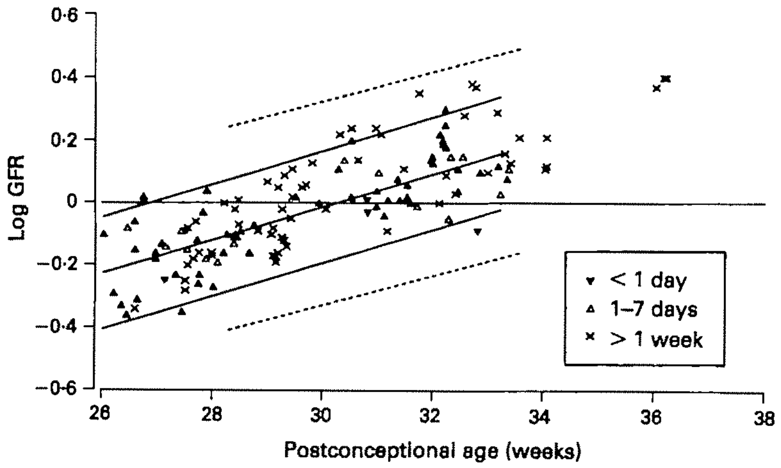

Figure 2 Log$_{10}$ transformation of fig 1 for three age groups (postnatal age) The diagonal solid lines are the regression line ±2 residual SDs (approximate 95% tolerance limits) for those points which are the first for each baby in the first postnatal week but older than 24 hours (n=36) The regression line is. Log$_{10}$ GFR (ml/min)=−1 615+0·0534× postconceptional age (weeks). The dashed lines show the approximate 95% tolerance limits recalculated from Coulthard (1985)[2] for the first measurement in the first week

Six subjects did not have respiratory distress syndrome, 16 had severe respiratory distress syndrome with an alveolar-arterial oxygen partial pressure difference (AaDpo$_2$) greater than 13·3 kPa (100 mm Hg) at any time. Only two did not receive assisted ventilation. Three babies died while being studied and two died later. No patient had anuria, haematuria, or proteinuria or any other evidence of acute tubular necrosis before or during the studies.

A total of 135 measurements of PF-S clearance were made in 39 infants, between the ages of 0·5 and 33 days. On 37 occasions the single injection method was used and in the remainder the constant infusion method. Both methods have been described previously.[13–15] For the single injection method 200 mg/kg PF-S was injected intravenously smoothly over 3–6 minutes. Samples of 0·1 ml arterial blood were taken at 10, 40, 80, 120, 180, 360, and 480 minutes and GFR calculated from the area under the concentration time curve by:

GFR=PF-S injected/area under curve

For the continuous infusion method a 25 mg/ml solution in water was infused intravenously at 0·6 ml/kg/hour through a 0·22 µm filter using a Graseby MS2000 syringe pump accurate to ±1%. For the first eight hours of the infusion, the infusion rate was at exactly double this final infusion rate which was then continued for 24 hours or more before 0·6 ml blood samples and fresh voided urine samples (aspirated from cotton wool balls) obtained. If the infusion ever became extravascular the cannula was replaced within one hour and at least six hours added to the infusion time before sampling. GFR (ml/min) and urine flow rate (urine volume or renal water excretion rate, ml/day) were calculated by:

GFR=PF-S infusion rate/plasma PF-S concentration

Urine flow rate=PF-S infusion rate/urine PF-S concentration

Urea excretion rate (mmol/day) was calculated by:

Urea excretion=urine flow rate×urine urea concentration

PF-S concentration was measured in duplicate 13 µl samples of plasma, diluted urine, or infusate using a modification by the author of the cysteine/tryptophan/sulphuric acid method with an alkali denaturing step to remove interfering sugars.[14–16] This method is highly sensitive and specific and the coefficient of variation was less than 2% for sample concentrations of 0·1 to 0·5 mg/ml.

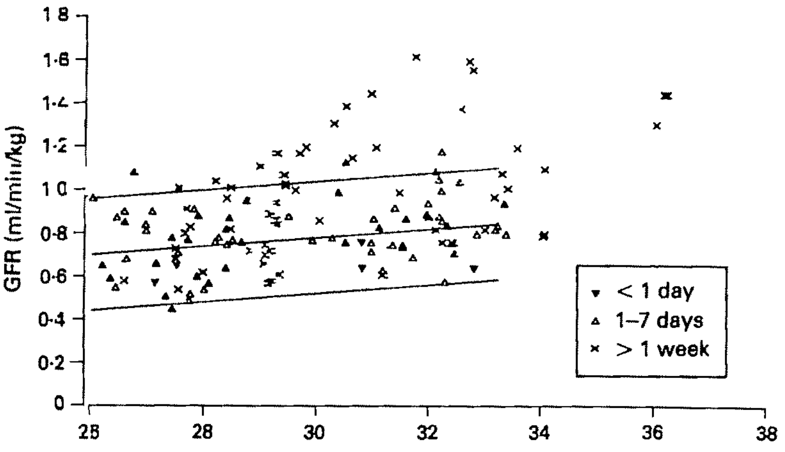

Figure 3 GFR factored by either birth weight or latest weight (whichever is the greater) as a function of postconceptional age (n=135). The diagonal solid lines are the regression line ±2 residual SDs (approximate 95% tolerance limits) for those points which are the first for each baby in the first postnatal week but older than 24 hours (n=36). The regression line has the formula: GFR (ml/min/kg)=0·167+0·0205 × postconceptional age (weeks)

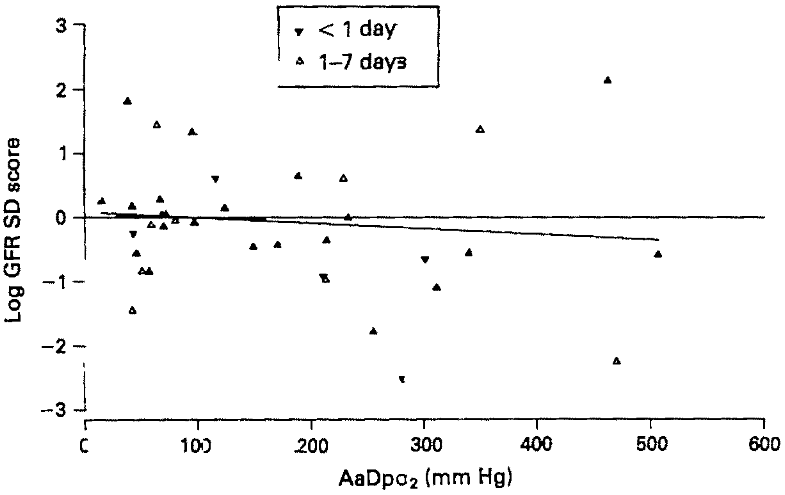

Figure 4 SD score (vertical distance from regression line) for the points in fig 2 for those aged 1–7 days as a function of AaDpo$_2$ (n=31). The regression line has the formula: GFR SD score=0·084–0·00087×AaDpo$_2$ (mm Hg). Five measurements at <1 day are also shown

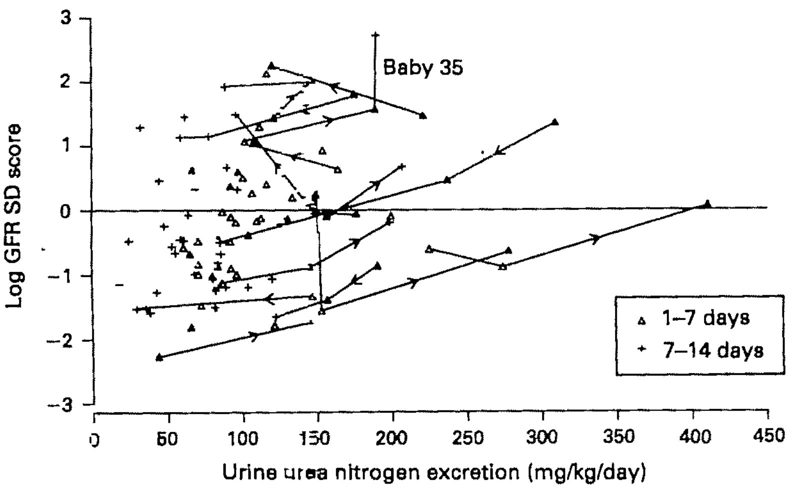

Figure 5 SD score (vertical distance from regression line) for the points in fig 2 for those aged 1–14 days as a function of urine urea excretion (n=98) Points are joined for some individuals with timing indicated by arrows. The regression line is not shown because the data are a mixture of cross sectional and longitudinal.

Results

Figure 1 shows all the results for GFR plotted against postconceptional age. This scattergram and figs 2, 4, and 5 include a mixture of cross sectional and longitudinal data. There is a steepening increase in GFR with increasing postconceptional age between 26 and 34 weeks. The relationship is approximately exponential (fig 2). The range of raw GFR widens with increasing postconceptional age whereas the range of the logarithm of GFR is approximately constant. The geometric mean of GFR is 0·59 ml/min (95% tolerance interval 0·40 to 0·90 ml/min) at 26 weeks' postconceptional age and 1·40 ml/min (0·90 to 2·10) at 33 weeks.

The diagonal continuous lines in fig 2 are the logarithmic least squares regression line and the approximate 95% tolerance limits (mean ±2 residual SDs) for all those points which represent the first measurement made in each of 36 infants at less than 1 week of age but greater than 24 hours. This avoids bias from the inclusion of multiple measurements from individuals. The regression slope, 0·053, is significantly different from zero (95% confidence interval 0·039 to 0·067, $p<0·0001$).

Figure 3 shows GFR factored by body weight plotted against postconceptional age. Not all babies were weighed every day in which case the most recent weight was used, but if the infant's weight was less than the birth weight then the birth weight was used. This was the case in the majority of points on this graph. The regression line and tolerance limits are shown for the first measurement made on each baby at 1 day to 1 week, as in fig 2. The general relationship is linear for measurements less than 1 week, but these points are as a whole lower than those at greater than 1 week which confirms that in the majority of individuals GFR factored by weight increases more steeply with age. GFR in the first week increased only little from arithmetic mean 0·70 ml/min/kg (95% tolerance interval 0·45 to 0·95) at 26 weeks to 0·84 ml/min/kg (0·59 to 1·09) at 33 weeks. The regression slope, 0·0205, is only just significantly different from zero (95% confidence interval 0·0004 to 0·0406). This slope is reduced to zero if GFR is factored not by weight but by weight raised to the power 1·3 (weight$^{1\cdot3}$).

Five measurements made by single injection PF-S clearance between 12 and 24 hours of age all fall within the tolerance interval for later measurements in the first week, although low in the range, suggesting that the immediate rapid postnatal increase in GFR to its final level occurs in about 24 hours.

For the 36 first week measurements a SD score has been calculated for GFR from fig 2, being the vertical distance in residual SDs from the regression line. This is plotted in fig 4 against simultaneously measured AaDpo$_2$ in 31 cases. The regression slope, −0·00087, is not significantly different from zero (95% confidence interval −0·00355 to +0·00181). Similarly, there was no relationship with arterial:alveolar oxygen partial pressure *ratio*, or with FIO_2, arterial PO_2, PCO_2, pH, or base deficit. There was no trend for the SD score to vary with the age at which the GFR was measured in the first week.

One baby who had a steeper than normal rise in GFR (No 35, fig 1) had a high amino acid input (>300 mg nitrogen/kg/day) and a high urea nitrogen excretion in the four days before the final measurements at the end of the first week. Another, number 41, had a high nitrogen input but low excretion. Baby number 25 had a fall in GFR but a high nitrogen input and low excretion. In order to investigate whether GFR is influenced by intravenous amino acid input, SD scores were calculated for all GFR measurements in the first two weeks from the regression in fig 2. Linear regression analysis was then used to show how these scores varied with nitrogen input in the preceding 24 hours, with urine urea nitrogen excretion, with the difference between nitrogen input and excretion, and with plasma urea concentration. All regressions were non-significant except for that for urea excretion (regression slope 0·0041, 95% confidence interval 0·0008 to 0·0074) where there was a tendency for higher urine urea excretion to be associated with higher GFR in the first week. This suggests that the urea load being excreted may have some effect on GFR, but is clearly not the only cause of variation between individuals. There was no relationship between plasma urea or recent nitrogen input and GFR.

Discussion

The constant infusion method assumes that the plasma inulin concentration is constant with the infusion rate of inulin equal to the urinary excretion rate. This steady state requires at least four hours in adults. The method has been validated in adults and newborns[13 17 18] and carries some advantage over the traditional method in that it avoids the need for timed urine collections which, in the absence of high urine flow rates, are liable to inaccuracy especially in very small subjects. However, it is most important that the assumption that infusion rate is equal to the excretion rate is justified. In the preterm newborn the time required after commencement of such an infusion may be up to 48 hours in some cases before plasma steady state is reached or 24 hours after a priming double rate infusion of eight hours.[14 15] Some studies have assumed that steady state is reached after periods of only a few hours, and their results may thereby by invalidated.[13] The single injection method is also reliable and accurate if sampling is continued for 8–10 hours after the injection and the laboratory inulin assay is very accurate and precise.[14]

MATURATION OF GFR

The present study supports the view that GFR increases in a programmed way,[1 2] at least from 26 weeks' gestation and from the second postnatal day, which is unaffected by the gestation at birth. In the majority of infants studied, GFR matures after birth slowly and progressively, irrespective of changes in body weight and of various pathological events including respiratory disease.

An impression is gained from fig 2 that the crosses and triangles are scattered in approximately the same distribution. This impression is supported in fig 1, where the lines joining successive measurements in individuals follow the general trend of the group as a whole, approximately parallel to the regression line. There are some exceptions where there is a steeper increase (for example babies 35 and 41) or shallower or even a decrease in GFR (for example babies 25 and 40) as postconceptional age increases. These exceptions may be due to genuine differences in the maturation of GFR, or may be partly explained by methodological imprecision.

Apparent rapid increases in GFR after birth are most likely to be due to cessation of growth and the factoring of GFR by a weight or surface area which is falsely low as in fig 3.[2 19] Weight loss is common after birth, particularly in preterm babies, even those who do not have serious illness. It is not surprising that there is an increase in GFR, unfactored by any parameter of body size, with increasing maturity, because in the last trimester of pregnancy there is rapid increase in fetal weight paralleled by an increase in kidney size. Although this maturation of GFR has been described here and by others as 'logarithmic',[1 2] this is in fact an arbitrary label which conveniently describes the steepening increase in GFR within the 25 to 40 weeks' postconceptional age range. There is no implication that the fetal GFR at a given postconceptional age is the same as that of an infant already born. The little information on GFR before birth suggests that GFR is lower and increases after birth rapidly to the level observed within these studies within 24 hours after birth.[20–22] At any given gestational age, therefore, the kidney before birth has matured such that it has the capacity to attain a normal postnatal GFR as soon as the postnatal circulatory changes have been effected after 24 hours. Even at gestations as low as 26 weeks the kidney has the capacity to assume its excretory role long before the fetus is in fact due to be born, and this capacity is achieved by the second postnatal day. Even the five measurements between 12 and 24 hours age fell within the 95% tolerance interval. It is unlikely that the maturation of GFR is caused by volume expansion and/or excessive sodium input because most infants were volume contracted despite moderate sodium supplementation since birth.

The results are very similar to those of Coulthard who measured GFR in 39 relatively healthy infants of gestation 27 to 40 weeks at birth using a 24 hour continuous inulin infusion technique.[2] Linear regression has been reperformed on Coulthard's original raw data.[2] When only samples from infants less than 34 weeks' gestation at birth are included, with no repeated observations, to make comparison with the present study more meaningful, the number of observations was 23. There is no difference between the regression (slope 0·0508, intercept −1·54) and that of the present study. Coulthard's tolerance interval is somewhat wider, shown by the dashed lines in fig 2. The apparent rapid postnatal increase in GFR/kg was abolished when the weight used to factor GFR was a projected weight (a theoretical weight as if growth continued at a normal intrauterine rate). Therefore the apparent acceleration of GFR/kg in some babies was due to a temporary cessation of body growth whereas the GFR continued to mature at an apparently preprogrammed rate. A similar exercise in the present study yields a similar result but is not illustrated because of the arbitrary nature of projected weight.

Similar results were also obtained by Al-Dahhan *et al* using creatinine clearance.[1] Between 28 and 42 weeks' postconceptional age, creatinine clearance increased in an approximately exponential fashion when uncorrected for body size. Their regression for log GFR against postconceptional age (slope 0·07) was just outside the 95% confidence intervals of the present study. The range was wider at lower gestations, but not as wide as that of Coulthard,[2] 0·35 to 1·1 ml/min at 29–30 weeks and 0·9 to 2·0 at 34 weeks. GFR seemed to increase rapidly from 32 weeks because of its approximately exponential shape. Their regression line for first week measurements was no different from those at more than 26 days, suggesting that GFR after birth depends on postconceptional age, not postnatal age, as in the present study where there are more measurements in infants less than 28 weeks' gestation and more sequential measurements than previously.

WEIGHT AS STANDARD FOR GFR

No attempt has been made in the present study to factor GFR by body surface area or a function of body length[23] because it has been shown that weight is the best standard.[19,24] All previous measurements of GFR in preterm infants emphasise that this quantity is low compared with more mature and older individuals. But what is meant by 'low' GFR in an immature infant? Even when corrected for *projected* weight as in Coulthard's study[2] GFR is lower in the most immature subjects than more mature. This may be accounted for by the lower metabolic rate of the more immature individuals who should be growing fast. Growth has been described as a 'third kidney', because it reduces the need for renal nitrogen excretion.

The relationship between GFR and body size is complex. It is conventionally accepted that GFR is most likely to relate to the basal metabolic rate, since the principal function of glomerular filtration is the excretion of waste products of metabolism. It is useful that in adults and older children metabolic rate correlates well with, and is proportional to, body surface area or weight$^{0\cdot 67}$.[25] Small *adult* mammals have higher metabolic rate/kg but this relationship does not extend to infants.[19] Barratt has argued that extracellular volume would be more appropriate because this is the domain which is actually filtered.[26] But this is illogical because the extracellular fluid is only an intermediate vehicle for excretion of metabolic by products. The *volume* of the extracellular fluid does not determine the concentration of metabolic waste products therein, but rather the *production rate* and the GFR (extracellular fluid concentration=production rate/GFR for a substance completely cleared by glomerular filtration). Intracellular fluid volume (if it could easily be measured) might be a better standard because it is likely that metabolic rate will be proportional to cell mass. In the present study GFR must be factored by weight[1,3] in order to abolish the trend with increasing postconceptional age. This is different from older children but not unexpected because more mature and therefore larger babies have a higher cell mass per kg.[27] It may therefore be inappropriate to refer to GFR as being *low* when in fact it is entirely appropriate for the infant's metabolic needs. It is a different matter when considering the excretion of drugs because the low GFR and the relatively high extracellular fluid volume will demand an increased unit dose and a longer interdose interval.

In practice, expressing GFR as factored by body weight (birth weight or latest weight, whichever is higher) will be the most valuable and easiest, so long as it is realised that this will result in different 'normal ranges' at different gestations, and at different ages, as seen in fig 3.

THE INFLUENCE OF PROTEIN INTAKE ON GFR

A further question is whether the postnatal increase in GFR that occurs despite the illness and weight loss of the infants is promoted by either the catabolic state with endogenous urea production or the exogenous nitrogen that is administered, and secondly whether sodium wastage may be in part caused or worsened by such a forced increased in GFR. High protein intake has been shown to increase GFR in healthy adults and infants,[28] suggesting that there is a renal reserve available to promote the excretion of increased nitrogenous waste. In healthy immature newborns, in the presence of an increased renal urea load there is an obligatory increase in urine osmolality (presumably caused by urea), GFR, and sodium excretion.[28] These findings suggest that high protein intake may not be desirable in sick immature infants who cannot anabolise the administered protein and who have high urea production and high plasma urea. The present study has not convincingly demonstrated an effect in sick very low birthweight infants. This needs further study but accurate nitrogen balances would be needed and total urine nitrogen should be measured, not just urea. Urea as a marker of renal function is further discussed in part 2.[29]

THE EFFECT OF RESPIRATORY FUNCTION ON GLOMERULAR FUNCTION

Although perinatal asphyxia has often been associated with acute renal failure in term infants, changes in renal function have also been found in preterm infants with milder degrees of hypoxia or acidosis. The literature on renal function in infants with respiratory distress syndrome is mixed and confusing, some reporting no reduction in GFR, others that such babies have poor renal function.[8 30–35] The pathophysiological changes associated with hyaline membrane disease, including asphyxia, hypotension, poor tissue perfusion and acidosis, are thought to account for what has been called this functional renal failure in such infants. The apparent decrease in GFR appears to be related to the severity of the respiratory distress syndrome and has been thought to be partly responsible for the impairment of free water excretion. This is a little difficult to interpret because the problem is really confined to the first few days after birth when the methods for measuring GFR may not be reliable. None of the babies in the present study developed any reduction in GFR despite many having birth asphyxia or severe respiratory disease later. Other factors including antidiuretic hormone, atrial natriuretic peptides, adenosine, and prostaglandins are likely to be involved in the genesis of oliguria.[36–38] This will be considered further in part 3.[39]

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Renal function in sick very low birthweight infants: 2. Urea and creatinine excretion

Barry H Wilkins

Abstract

Plasma urea and creatinine concentrations and urea and creatinine clearances and excretion were measured in a sample of 40 infants of 25·5–33 weeks' gestation, birth weight 720–2000 g, between the ages of 0·5 and 33 days. Creatinine excretion rate was between 60 and 120 µmol/kg/day in the first five postnatal weeks (mean 90·5) and was independent of sex or growth retardation. This can be used in clinical practice to estimate instantaneous urine flow rate V, if the creatinine concentration is measured in a randomly voided urine sample, from the formula V=90·5/urine creatinine, with 95% confidence limits ±39%. There is a wide range of plasma creatinine at all gestations and ages decreasing from range 75–130 µmol/l in the first two days to 35–80 µmol/l at 3 weeks of age. Plasma urea is a poor indicator of glomerular filtration rate (GFR) in sick preterm infants. GFR (ml/min/kg) can be estimated from plasma creatinine from the formula GFR=69·2/plasma creatinine but this estimate is imprecise with 95% confidence limits ±46%. Urea:creatinine clearance ratio was usually less than 1·0 (range 0·18 to 1·5) and was lower when the urine flow rate was low. Urea excretion was up to 17 mmol/kg/day in the first two weeks, higher in the more immature infants. These high levels were paralleled by a high plasma urea concentration, up to 18 mmol/L. A high plasma urea is not necessarily associated with renal failure or dehydration.

(*Arch Dis Child* 1992;67:1146–53)

The clinical management of sick preterm infants requires meticulous attention to many aspects of physiology and to the daily prescribing of water, salts, and nutrition. Renal physiology often receives scant attention because plasma creatinine is the only accessible index of renal function, and even this may be unreliable because of interfering substances in routine methods. Although urine is easily obtainable it is rare for neonatal units to measure urinary indices of renal function routinely. In prescribing intravenous water and electrolyte treatment it may be useful to have a day to day, or even more frequent, estimate of renal excretion of water, sodium, potassium, etc. Such an estimate may be obtained without the tedium and inaccuracy of timed urine collections by relating urine concentration to creatinine, provided creatinine excretion rate is not scattered too widely. The few reports of creatinine excretion so far are not encouraging in this respect[1–6] but most have relied on timed urines for their measurement. Plasma urea is a poor guide to glomerular function in all subjects but has received little attention in the sick preterm newborn.

The purpose of the present investigation was: (1) to establish a normal range for plasma creatinine in sick infants less than 33 weeks' gestation at various ages using a creatinine method which measures true creatinine without interference; (2) to establish a normal range for creatinine excretion and thereby derive formulas to estimate glomerular filtration rate (GFR) and urine flow rate from plasma and urine creatinine; and (3) to investigate the usefulness of plasma urea as an indicator of renal function by examining the relationship between urea and creatinine clearance and between plasma urea and urea excretion.

Patients and methods

This study was part of a wider study of glomerular and tubular function in very low birthweight infants. Altogether 40 infants were chosen who could be studied in the first postnatal week, and later if possible. Gestation at birth was 25·5–33 weeks, birth weight 720–2000 g. Further clinical, experimental, and laboratory details are given in part 1.[7]

Plasma creatinine and urea concentrations were measured sequentially in 40 infants up to age 3–33 days. Urine flow rate was measured on 124 occasions in 39 infants by a continuous infusion Polyfructosan-S (PF-S, Laevosan-Gesellschaft) clearance method,[8 9] between the ages of 0·5 and 33 days. Urine flow rate (urine volume or renal water excretion rate, ml/day) was calculated by:

Urine flow rate=PF-S infusion rate/urine PF-S concentration

Creatinine excretion rate (µmol/day) was calculated by:

Creatinine excretion=urine flow rate×urine creatinine concentration

Urea and sodium excretion rates (mmol/day) were similarly calculated. Plasma and urine creatinine were measured by a modification[8] of a resin adsorption method[10 11] which avoids the positive interference of non-creatinine chromogen and the negative interference of

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bilirubin. The resin adsorbs creatinine but not substances that normally interfere with the Jaffé creatinine assay. Approximately 6 mg Dowex 50W-X8(H) 200–400 mesh ion exchange resin is added to the samples. After 15 minutes the resin is washed twice and the creatinine eluted with 600 µl alkaline picrate. The optical density of the supernatant is measured at 515 nm. The reaction is linear and for a plasma creatinine of 100 mmol/l optical density is 0·068. The coefficient of variation is 4·4% at 69 µmol/l and 2·4% at 499 µmol/l. Yield for creatinine added to plasma or urine was 95–105%. Bilirubin, glucose, proteins, and ketones did not interfere.

Plasma urea was measured by an enzymatic colorimetric method on a Technicon RA-1000 multichannel discrete autoanalyser where ammonia is produced from urea by a urease enzyme and combines with 2-oxoglutarate and NADH to yield L-glutamate and NAD. The coefficient of variation is 2·7% at 2·5 mmol/l and 1·1% at 17 mmol/l. Urine urea concentration was measured on a Technicon SMAC 3 system by a photometric method which depends on the formation of a chromophore by the combination of urea with diacetyl in acidic solution in the presence of ferric ions and thiosemicarbazide. The coefficient of variation is 0·7% at 12 mmol/l and 4·5% at 2 mmol/l. Urine sodium and potassium were measured by photometry (Instrumentation Laboratories 913) and osmolality by cryoscopy (Gonotec Osmomat 030), all with a coefficient of variation of <1%.

Urine flow and sodium, creatinine, and urea excretion rates were expressed as ml, mmol, or µmol/kg/day. Weight rather than surface area was used because it is physiologically more appropriate in immature infants[12] and it is more accessible in routine practice. Birth weight was used unless the baby had regained his birth weight and was growing in which case latest weight was used. Factoring by a weight less than birth weight causes false overestimation of renal functions.[7 13]

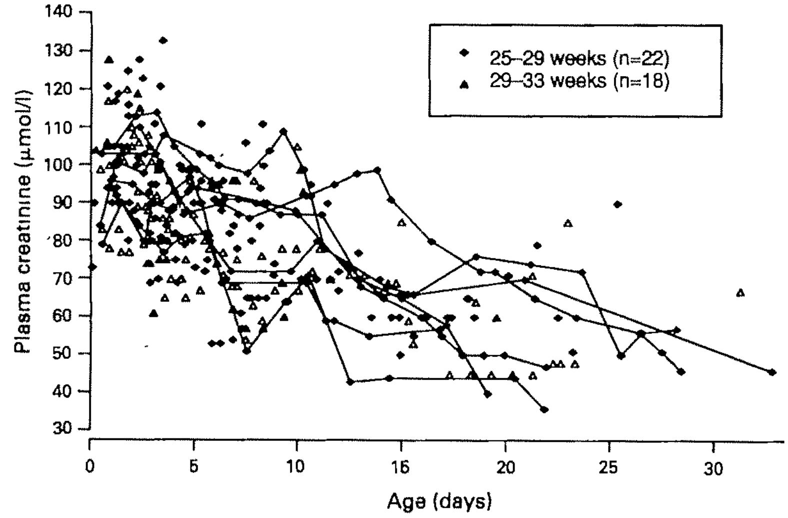

Figure 1 Plasma creatinine concentration (resin adsorption method) as a function of postnatal age for two gestational groups (n=367). Sequential measurements are joined for six individuals

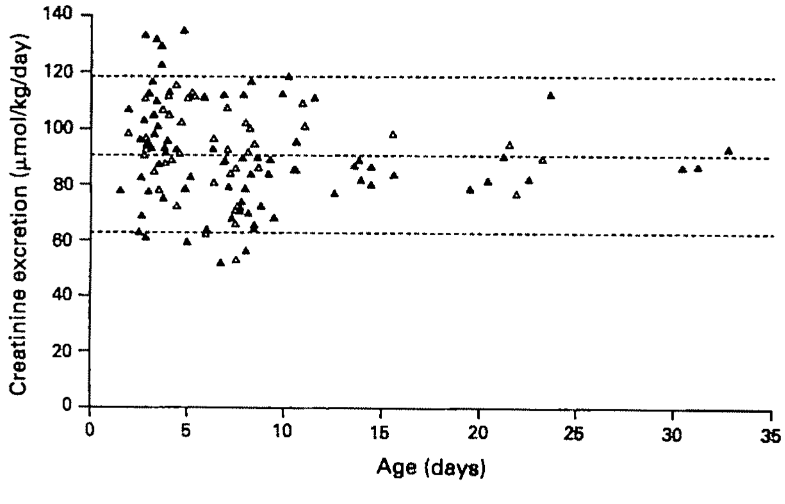

Figure 2 Creatinine excretion rate as a function of postnatal age (n=123). Repeated measurements in individuals are included. The dotted horizontal lines are the mean (90·5 µmol/kg/day) ±2 SDs for all measurements

Results

PLASMA CREATININE

Plasma creatinine as a function of age is shown in fig 1. This scattergram and all other figures include a mixture of cross sectional and longitudinal data. There is a wide variation at all ages with an overall decline during the first two to three weeks. Points are joined for six individuals studied for longer than two weeks. In some infants the creatinine has reached a trough by the third week, but in others it is still declining. There is an initial steep decline in the first week in most infants, although this is sometimes preceded by an initial increase. This is presumably because the result in the first day or two reflects maternal creatinine.[14 15] There is a wide overlap between the ranges in the two groups shown. Means and their 95% confidence limits were calculated for the two groups at the ages: <2 days, 3rd day, 4th day, 4–7 days, 7–14 days. Only at the 4th day and 4–7 days were there significant differences between the means shown in the table.

CREATININE EXCRETION RATE

Creatinine excretion rate as a function of postnatal age is shown in fig 2. At all postnatal and all postconceptional ages there is a broad

Mean plasma creatinine concentration (µmol/l) at various postnatal ages in infants of two gestational age groups The 95% confidence intervals for the means are shown in parentheses

Age	*25 5–29 weeks*	*>29–33 weeks*
<2 days	101 (94 to 108) [n=17]	103 (95 to 111) [n=12]
3rd day	98 (90 to 106) [n=17]	94 (88 to 100) [n=14]
4th day	97 (90 to 104) [n=19]	84 (76 to 92) [n=13]
4–7 days	88 (84 to 92) [n=20]	82 (77 to 87) [n=13]
7–14 days	82 (72 to 92) [n=18]	75 (66 to 84) [n=13]

range of excretion rates, the range being wider in the first week when more observations were made. Multiple estimations in individual babies were averaged for the first week postnatal and for after the first week. Mean creatinine excretion in the first week (30 babies) was 91·9 µmol/kg/day, and mean excretion after 1 week was 89·4 µmol/kg/day. There was no significant difference between these. The difference between first week creatinine excretion and later creatinine excretion in individual babies had a range of −32 to +32 µmol/kg/day, mean 2·5 (95% confidence interval −6 to +11). Creatinine excretion increases significantly with postconceptional age within the range 26–33 weeks, from 81 µmol/kg/day at 26 weeks to 102 µmol/kg/day at 33 weeks. No inference can be made outside this range of postconceptional age. Infants whose birth weight was less than the 50th centile for gestational age had the same excretion rates as those with birth weights greater than the 50th centile.

Mean overall creatinine excretion was 90·5 µmol/kg/day (62·8 nmol/l min) with a SD of 14 µmol/kg/day. The distribution is normal. The approximate 95% tolerance interval (mean ±2 SDs) is 62·5 to 118·5 µmol/kg/day, shown as horizontal dashed lines in fig 2. The maximum change in any baby, 32 µmol/kg/day, is less than the 95% tolerance interval, suggesting that each individual kept the creatinine excretion rate within narrower boundaries than the group as a whole.

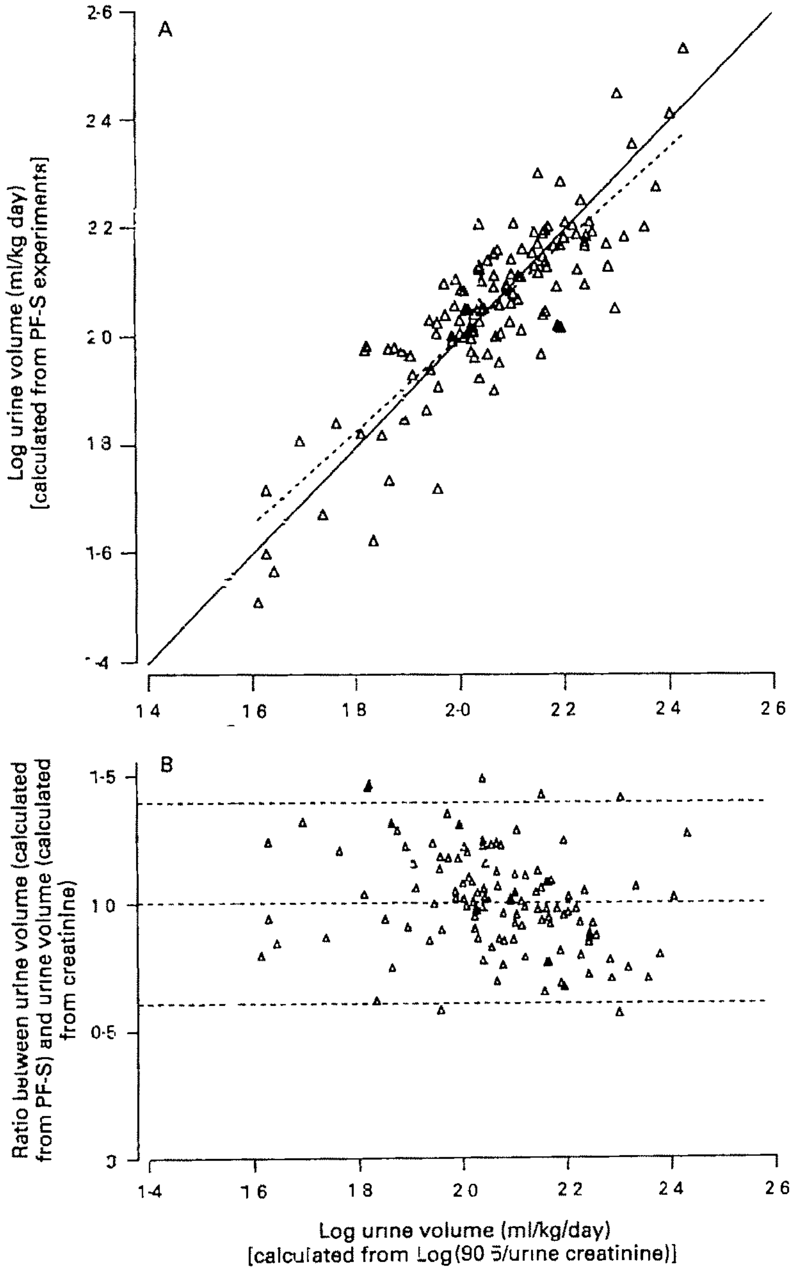

Figure 3 (A) Upper panel: urine volume (flow rate) calculated from 123 PF-S infusion experiments plotted against estimated urine volume calculated from 90·5/urine creatinine concentration The points are plotted as the logarithmic transformation for clarity The diagonal lines are the line of identity and the linear regression line, y=0·27+0 87x (B) Lower panel: the ordinate is the ratio between urine volume measured in PF-S experiments and estimated urine volume calculated from the urine creatinine. The ordinate is near to a normal distribution with the mean (1 0) and mean ±2 SDs shown as dotted lines.

ESTIMATING URINE VOLUME FROM URINE CREATININE AND GFR FROM PLASMA CREATININE

Figure 3A shows urine flow rate (urine volume or water excretion rate) measured in PF-S infusion experiments plotted on the ordinate against urine flow rate estimated simultaneously from urine creatinine. Estimated urine flow rate (ml/kg/day) is calculated from the formula 90·5/urine creatinine (µmol/l), where 90·5 is the overall mean creatinine excretion rate in µmol/kg/day. The difference between the two values is because the actual creatinine excretion rate is not equal to the mean value of 90·5 µmol/kg/day. The data are plotted logarithmically for clarity, not for any statistical reason. A more complicated formula could have been used, based on the regression line, but not with any useful increase in precision. The precision of this formula for estimated urine flow (90·5/urine creatinine) is tested by examining the ratio between measured and estimated urine flow rate, shown in fig 3B plotted on the ordinate. The untransformed ratio is plotted rather than its logarithm (the vertical distance of the points in fig 3A from the line of identity) because the untransformed value has the most nearly normal distribution. The 95% confidence limits (mean ±2 SDs) for urine flow rates are the estimated value ±39%, shown as the horizontal dashed lines in fig 3B.

GFR (ml/kg/min) can similarly be estimated from mean creatinine excretion and plasma creatinine (µmol/l) from the formula 90·5×1·101/1·44/plasma creatinine (69·2/plasma creatinine), where 1·101 is the mean ratio, in the present study, between GFR and creatinine clearance.[16] The confidence limits are somewhat wider, ±46%, because of the introduction of this extra variable factor and also greater imprecision in measuring plasma creatinine.

An estimate of urine flow rate is useful in clinical practice in order to estimate renal excretion of urine constituents such as sodium ($E_{Na}=U_{Na}\times$urine flow rate). Urine sodium concentration (U_{Na}) alone is an unreliable indicator of sodium excretion, because it also depends on urine flow rate. Figure 4 shows a more than 5-fold variation in sodium excretion rate, 3 to 20 mmol/kg/day, on occasions when urine sodium concentration is high, around 150 mmol/l, and more than 10-fold, 0·5 to 7 mmol/l, when urine sodium is low, 10 mmol/l. Similarly, urine osmolality is not a useful inverse indicator of urine flow rate compared with urine creatinine concentration. High osmolality urine (>500 mosmol/kg) was observed with high as well as low urine flow rates and in the former case was associated with high excretion of other solute such as sodium.

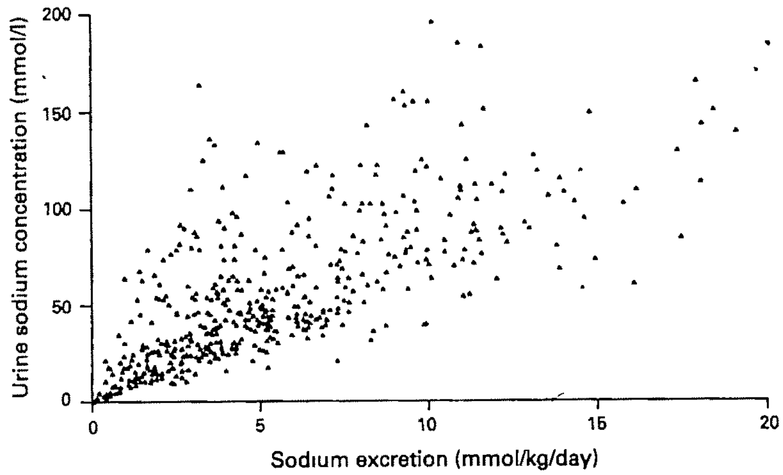

Figure 4 Urine sodium concentration as a function of sodium excretion rate in 471 urine samples. The latter was either measured in PF-S experiments (n=124) or calculated from urine creatinine concentration (n=347)

UREA AND CREATININE CLEARANCES COMPARED

Figure 5 shows urea and creatinine clearances compared. Urine/plasma (U/P) ratios are plotted rather than clearance (UV/P) in order to eliminated the common variable V (urine volume). In the majority of samples U/P urea ratio is lower than that for creatinine, and there is wide scatter. Urea clearance varies from 0·18 to 1·5 times creatinine clearance. The logarithmic transformation is plotted to produce a distribution suitable for linear regression which shows that there is a tendency for urea clearance to be lower at low urine flow rates (regression slope 0·70, 95% confidence interval 0·64 to 0·75, $p<0·0001$). Urea is presumably reabsorbed by the renal tubule in a very variable manner, more in oliguric infants.

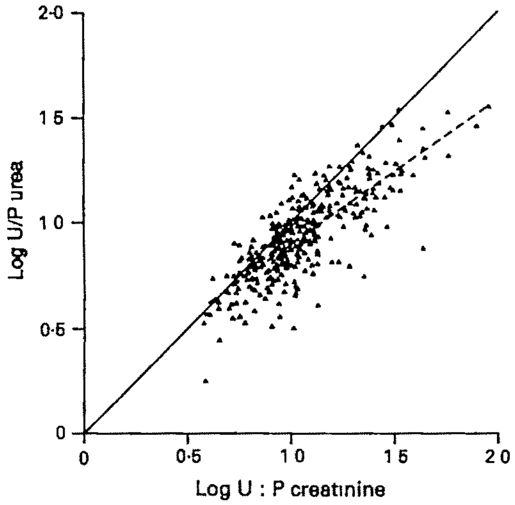

Figure 5 U/P ratios for urea and creatinine compared. Both axes are logarithmic for clarity and so that the distribution is suitable for regression analysis (n=324). The diagonal lines are the line of identity and the linear regression line, U/P urea=0·20+0·70×U/P creatinine.

UREA EXCRETION AND PLASMA UREA

Plasma urea (fig 6) varied widely, from 0·3 to 18 mmol/l and values tended to be high throughout the whole of the first two weeks. Urea excretion follows a similar pattern with levels 0·6 to 17 mmol/kg/day. Individual sequential graphs show a pattern of a postnatal rise and fall over 1–3 weeks (fig 7). The peak excretion rate (range 2·5 to 17 mmol/kg/day) and peak plasma urea concentration (range 3·6 to 18 mmol/l) for each baby and the age at which they occurred were chosen as summary measures.[17] The peak occurred between the first and 10th day at all gestations but was higher in the most immature. There was a significant negative relationship between peak urea excretion rate and gestational age (regression slope −0·59, 95% confidence interval −0·97 to −0·21, $p<0·05$) and between peak plasma urea and gestational age (regression slope −0·62, 95% confidence interval −1·06 to −0·18, $p<0·01$). Although there was no relationship between the time of the peak and gestational age, the time of the urea excretion and plasma urea peaks in individuals correlated highly significantly (Pearson's $r=0·58$, 95% confidence interval 0·32 to 0·76, $n=39$, $p=0·0002$). Similarly the magnitude of the peaks correlated significantly in individuals ($r=0·66$, 95% confidence interval 0·44 to 0·81, $n=39$, $p<0·00005$).

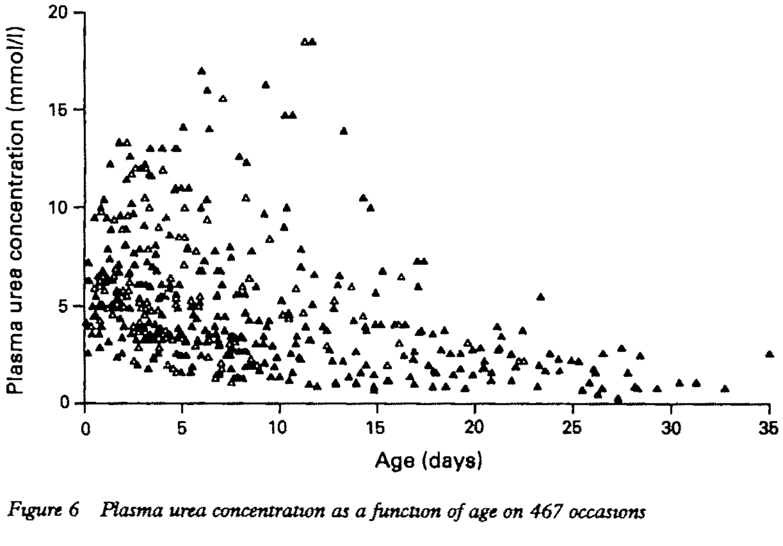

Figure 6 Plasma urea concentration as a function of age on 467 occasions

Nitrogen input (as Vamin, KabiVitrum) was low until the fourth day in most infants. There was no relationship between nitrogen input and urea nitrogen excretion, with input ranging from 0 to 400 mg/kg/day at all urea

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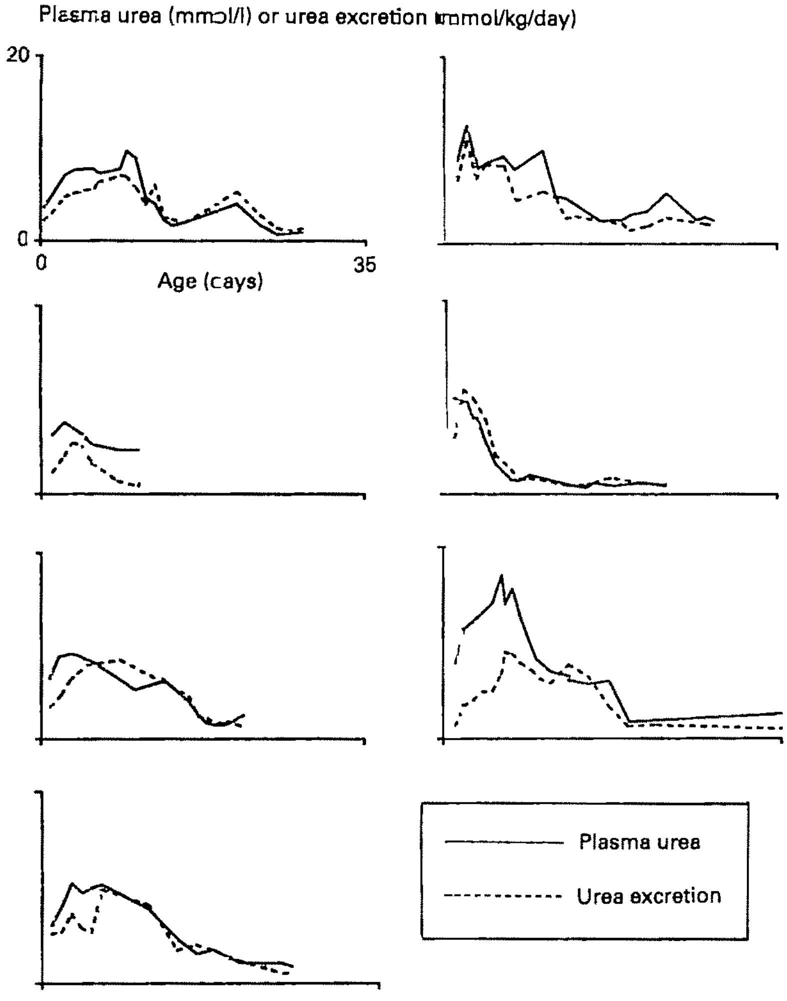

Figure 7 Plasma urea concentration and urea excretion as a function of age for seven infants <28 weeks' gestation.

excretion rates, and similarly none between nitrogen input and plasma urea. The presence of high urea excretion with zero or low nitrogen input on many occasions suggests that many of these infants particularly in the first one or two weeks postnatally are catabolic with respect to protein. In the absence of a high nitrogen input it is likely that the high plasma urea concentrations are caused by the high urea production. Urea production rate by cells was not calculated (from nitrogen excretion and change in plasma urea). In some infants urea nitrogen excretion exceeded input in the second and even third weeks.

Discussion

CREATININE EXCRETION

Creatinine excretion in preterm neonates in the present study is similar to previous estimates of mean 71,[3,4] 60–80,[6] 85,[2] 95,[1] and 100 μmol/kg/day.[5] Only two have emphasised the small but significant increase through the last trimester.[3,6,18] In all these studies the range is wider than in the present study; in one the range was about 18 to 180 μmol/kg/day,[3] in others 45 to 180,[1] 57 to 143,[5] and approximately 30 to 230.[2] The narrower range in the present study may be due in part to the clinical and laboratory methods used.[5,16] The differences in the means may be due to different creatinine methods or methods of estimating or measuring urine flow rate or different postconceptional age of the infants. Creatinine methods should not be inaccurate for urine creatinine because there is no non-creatinine chromogen; however the author has found that some routine laboratory methods measure aqueous standards with inaccuracy up to 20% (B H Wilkins, unpublished observations). One of the above studies used polyfructoside as marker of urine flow[5]; the others measured timed urine collections with the inherent difficulties with that technique. The higher mean of 95–100 μmol/kg/day in two studies[1,5] may be accounted for partly by the higher mean gestational age (31 and 33 weeks compared with 29 weeks here). Three[1,3,5,18] found no significant relationship between creatinine excretion and postconceptional age but at least two of these[1,3,18] considered correlation coefficient instead of regression slope. The variables correlated did not have normal distributions. Correlation is for comparing two independent variables; here we are examining how one variable depends on another. They also apparently ignored bias from multiple measurements in individuals.

Creatinine excretion rate is lower when expressed in terms of body weight than older babies[2,3,19] and children (B H Wilkins, unpublished observations), even more so when expressed in terms of height or surface area. Weight is chosen as reference because creatinine output is related to muscle cell mass,[1,19,20] which intuitively relates best to weight. Cell mass, or intracellular fluid volume, and basal metabolic rate are lower in preterm infants than term and older infants,[21,22] and this may account for the lower values in the more immature.

Creatinine *production* rate could be estimated from *excretion* rate and rate of change of plasma creatinine, but requires also knowledge of creatinine distribution volume (total body water). Although non-renal elimination is probably minimal, the wider range of creatinine excretion in isolated urine samples in the first week may be because plasma creatinine concentration is rising or falling. No attempt has been made to estimate production rate. The present concern is to derive useful and simple formulas based on urine creatinine.

ESTIMATING URINE VOLUME AND GFR

Although there is a significant increase in creatinine excretion with postconceptional age, formulas have been derived for estimating GFR (based on plasma creatinine) and urine volume (based on spot urine creatinine) which are common to all sick preterm infants in the first 2–3 weeks in whom these quantities might be useful. The numerator in these formulas contains 90·5, the overall mean creatinine excretion (μmol/kg/day). Improved accuracy and precision would be obtained by applying a variable creatinine excretion from 81 at 26 weeks postconceptional age to 102 at 33 weeks but this would make the calculation more complicated for little useful gain. These formulas will apply so long as the laboratory creatinine method measures aqueous creatinine standards accurately. Neonatal units should check this. The imprecision of the urine flow rate estimate, ±39%, is much lower than the overall variation in urine flow which is >10-fold; urine creatinine concentration ranges from 300 to 4000 µmol/l. The only reliable way of *measuring* urine flow is to weigh nappies meticulously, but even this does not preclude escape of urine.

Coulthard *et al* have derived similar formulas but calculated an asymmetric 95% confidence interval (–35% to +53%) from the scatter around the regression of *logarithmically* transformed urine volume on log estimated urine volume, but did not show that the data were normally distributed about the regression line.[5] It is unlikely that they were, as in the present study. Plotting the logarithmic transformed data does render the distribution of urine volume nearer to normal and standardises variances, but this is only useful when calculating correlation coefficients which is not an appropriate statistical approach to comparing two measures of the same variable.[23]

The estimate of urine flow and sodium excretion on spot urines does not measure 24 hour excretion, and does not solve the whole problem of prescribing fluids, but gives a guide to the situation at the time. It is a quick and easy addition to daily weight change and plasma sodium to help make sensible decisions about water and sodium requirements.

The GFR estimate is more imprecise and less useful. Plasma creatinine concentration is a more direct indicator of glomerular function and normal ranges are available from the present study and others.[24–26]

Formulas based on height and plasma creatinine estimate GFR factored by surface area.[2 27] This may be useful in older children but has been shown to be inappropriate in infants.[7 8 12] The validity of these formulas was based on a significant correlation coefficient between the formula derived estimate of GFR and a 24 hour creatinine clearance. It is not surprising that the two quantities are *correlated* but inspection of the data shows wide individual differences between the estimated GFR and creatinine clearance.[2 27] Inspection of their graphs shows that the estimate of GFR/m^2 was 35% to 280%[27] and approximately 50% to 300%[2] of the measured creatinine clearance which hardly inspires confidence in such a formula.

PLASMA CREATININE

Plasma creatinine in the present study is similar to published normal ranges.[24–26] Rudd *et al* found little difference between infants less than 28 weeks and those 28 to 32 weeks' gestation.[24] Their median was 104 mmol/l at 2 days for <32 week gestation infants, 84 at 7 days, 72 at 14 days, and 60 at 21 days. Their range is wider at all ages, for example 95% tolerance limits of ±50 to ±60 µmol/l at 7 days compared with no more than ±30 µmol/l in this study. This may be because of a more precise and accurate assay with less interference from positively and negatively interfering substances. Any 'normal range' is clearly method dependent. The sick patients in the present study did not have higher creatinines than the more healthy individuals of previous studies, even those with severe respiratory disease. This accords with the finding of no reduction in GFR in patients with severe respiratory disease.[7] Further, the decline with increasing age is not complete until 1 month.

Plasma creatinine is influenced by the following: (1) the increase in glomerular filtration rate with age[7 13]; GFR increases postnatally despite the lack of body growth whereas creatinine excretion is related to cell mass which is itself static after birth until weight gain begins. The postnatal weight loss is caused largely by loss of extracellular volume, not loss of cell mass. (2) The increase in cell mass as a proportion of body size as babies grow. (3) The fact that in the early neonatal period plasma creatinine reflects maternal plasma creatinine,[14 15] accounting for a rise or fall in the immediate postnatal period. (4) Variable transfer of creatinine across the renal tubule.[2 5 8 16 28–30] (5) Differences in and the imprecision of laboratory methods. It is not surprising, therefore, that plasma creatinine changes in ways which cannot be fully understood.

The lack of any results greater than 130 µmol/l suggests that this may be used as an upper limit of normal (using this laboratory method) in the first few postnatal days for the diagnosis of neonatal renal failure, and there is no need to quote a different figure for different gestations, at least in infants born at less than 33 weeks. However, plasma creatinine will increase slowly after the onset of acute renal failure. Creatinine is distributed in total body water, so when there is an abrupt change in GFR it may take several days for plasma creatinine to reach a new steady state level. The half time of these changes is approximately proportional to volume of distribution divided by GFR. For a volume of distribution of 80% of body weight and a GFR of 0·5 ml/min/kg this half time will be about 18 hours.

Most routine laboratory methods for creatinine use one of many kinetic Jaffé methods which reduce but do not eliminate the over estimation caused by non-creatinine chromogen.[5] A further problem in newborns is negative interference caused by bilirubin.[31] It should be borne in mind that day to day changes in apparent plasma creatinine might in part be due to changes in plasma bilirubin. This is not the case here where a resin adsorption end-point Jaffé method has been used but individual units should check their method.

PLASMA UREA AND UREA EXCRETION

Urea excretion rates are very much higher than in older children and adults where it is less than 1 mmol/kg/day. The presence of high urea excretion in the absence of any nitrogen input suggests that many of these infants particularly in the first one or two weeks postnatally are catabolic with respect to protein. This is likely to reflect their general state of ill health[6] and it is notable that it is accompanied by a high plasma urea concentration. The levels found here are greater than found previously in more mature infants, even those ill with birth asphyxia or respiratory distress.[32 33]

A high plasma urea concentration may in part be explained by a low urea clearance as in dehydrated, oliguric older subjects where there is increased urea reabsorption in the collecting duct. However, the positive correlation between plasma urea, urea excretion, and negative nitrogen balance suggests that plasma urea closely reflects the urea excretion rate which itself represents the urea production rate by intracellular metabolism. Urea production rate, taking into account change in total body urea, has not been calculated here because body weight was not measured every day in all babies and because urea distribution volume can only be assumed. It is likely that peak urea production is greater than peak excretion because plasma urea is usually rising as excretion is rising. Others have estimated urea production up to 8 mmol/kg/day, declining after the age of 2 days.[6] It might be argued that the high urea excretion could cause an osmotic diuresis. However, the low urea clearance with tubular urea reabsorption may protect against this. This 'economy of water' is a specific feature of urea that has been known for a long time.[34 35] No evidence was seen of increased water excretion in infants with high urea excretion in the present study.

Urea clearance was compared with creatinine rather than PF-S clearance because there were many more occasions when both were measured and because it has been shown previously that creatinine clearance is a reasonable estimate of GFR.[2 5 7 16] Urea clearance tends to greatly underestimate GFR as found by others.[5 36 37] We agree with Coulthard *et al* that the measurement of urine urea is of little use in clinical practice.[5] Plasma urea concentration is of no use as a marker of glomerular function. It may, however, be useful in sick immature infants as an index of metabolic derangement or to demonstrate its contribution to hyperosmolality. No influence has been found of nitrogen input on urea excretion, but the possibility that a lower nitrogen input in those with high excretions might have lowered the plasma urea has not been tested. Others have shown that nitrogen is incorporated into tissue in sick preterm infants from the first day[38] but this does not conflict with the present study where formal nitrogen balances have not been performed. Plasma urea and urea excretion were not reported in that study. Urea production and plasma urea are high in the fetus.[39] Further investigations are needed to determine whether high rates of urea production are caused directly by postnatal illness or whether it is due to high urea production before birth and cessation of placental function at birth, and whether postnatal nitrogen and energy input influences plasma urea and nitrogen excretion.

This work was funded by the Children Nationwide Medical Research Fund, and the Southmead Research Foundation, Southmead Hospital, Bristol. The author is grateful to Mrs N Kingston and Mrs M Williams for performing some of the laboratory work, to Dr B Speidel, Dr P Fleming, and Professor P Dunn for allowing their patients to be studied, Dr T Chambers for continual encouragement, and Dr J P Midgley for inspiration in the final stages of writing

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Renal function in sick very low birthweight infants: 3. Sodium, potassium, and water excretion

Barry H Wilkins

Abstract

Renal excretion of sodium, water, and potassium was measured on 434 occasions in a sample of 40 infants of 25·5–33 weeks' gestation, birth weight 720–2000 g, between the ages of 0·5 and 36 days. Water excretion varied between 1% and 30% of the glomerular filtration rate, or 15–350 ml/kg/day, and varied widely from day to day in individual infants. Nearly all infants became hyponatraemic before or after the first postnatal week. There were a few instances of hypernatraemia in the first week caused by high insensible water loss. There were high levels of sodium excretion up to 16% of filtered sodium, or 21 mmol/kg/day, in the first two postnatal weeks. Highest levels of sodium excretion were seen in the most immature infants in the first week. In most infants sodium excretion increased either in the first week or later before a subsequent decline. Potassium excretion was often high in the first week, as much as 96% of filtered potassium, or 5 mmol/kg/day, and is associated with early hyperkalaemia.

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Preterm newborn infants have long been known to have difficulty in maintaining sodium balance on the sodium intake provided by human milk of 1–2 mmol/kg/day. This is related to excessive urinary excretion of sodium, which decreases with increasing gestational and postnatal ages and has been extensively reviewed.[1-5] Hyponatraemia is common[1-7] but its cause remains debated especially in the first week where water retention or sodium depletion may contribute.[1 4 6 7] This has caused controversy in management where some advocate sodium supplements,[4 8] others water restriction.[6 7 9 10]

The question is more serious in the smallest and sickest infants in whom hyponatraemia, excessive weight loss, or conversely failure to lose weight postnatally, hypernatraemia, hyperkalaemia, uraemia, and haemodynamically significant patent ductus arteriosus (PDA) are commoner. More information on water and electrolyte excretion is therefore needed to provide guidelines for treatment in the sickest and smallest infants.

The present study was conceived because of the observation of frequent water and electrolyte complications in such infants at all ages despite sodium supplementation as advocated for healthy preterm infants.[8] The purpose was to describe the various patterns of sodium, potassium, and water excretion which occur in very low birthweight infants, and to provide further information on the pathology and physiology of natriuresis in these infants.

Patients and methods

This study was part of a wider study of glomerular and tubular function in very low birthweight infants. Altogether 40 infants were chosen who could be studied in the first postnatal week, and later if possible. Gestation at birth was 25·5–33 weeks, birth weight 720–2000 g. Studies were made up to age 3–36 days. Further clinical, experimental, and laboratory details are given in part 1.[11] A total of 434 plasma/urine pairs were examined of which 120 were taken during continuous Polyfructosan-S (PF-S, Laevosan-Gesellschaft) infusion experiments by which urine flow was measured.[12] In the others calculations were made from urine and plasma creatinine.

Urine flow rate (renal water excretion) was calculated from either

$$\text{Urine flow rate (ml/kg/day)} = \text{PF-S infusion rate}/\text{urine PF-S concentration}$$

or, on days when there was no PF-S infusion experiment,

$$\text{Urine flow rate (ml/kg/day)} = \text{creatinine excretion rate}/\text{urine creatinine concentration}$$

where creatinine excretion rate is that measured in that baby in the nearest PF-S infusion experiments, or 90·5 μmol/kg/day (the overall mean creatinine excretion rate[13]) in two infants who did not have PF-S experiments.

Excretion rate of other substances was calculated, for example sodium excretion (E_{Na}), from

$$E_{Na}\ \text{(mmol/kg/day)} = \text{urine flow rate} \times \text{urine sodium concentration.}$$

Osmolar excretion (mosmol/kg/day) was calculated similarly from the urine osmolality.

Fractional excretion (percentage of filtered load) was calculated, for example fractional sodium excretion (FE_{Na}) from

$$FE_{Na} = U_{Na}/P_{Na} \times P_{PF\text{-}S}/U_{PF\text{-}S}$$

or

$$FE_{Na} = U_{Na}/P_{Na} \times P_{Cr}/U_{Cr} \times 1{\cdot}101$$

where 1·101 is the mean ratio in this study between inulin and creatinine clearance,[14] and corrects for tubular creatinine reabsorption. U and P represent urine and plasma concentrations.

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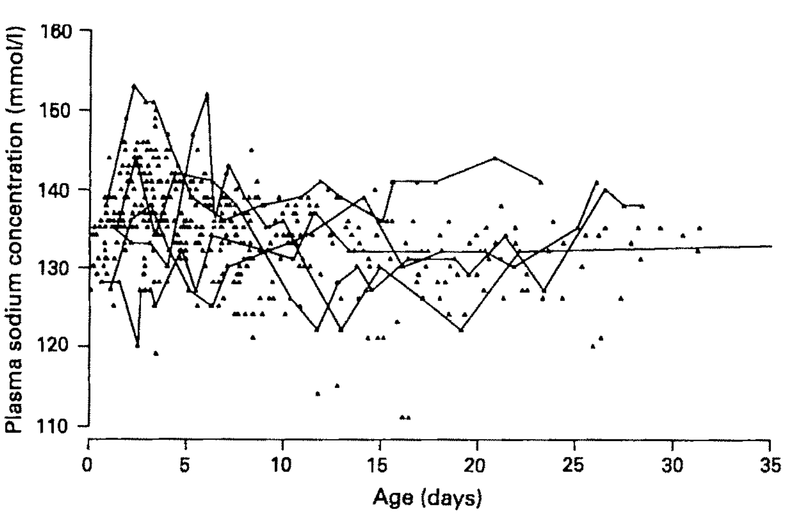

Figure 1 Plasma sodium concentrations as a function of postnatal age. Sequential points are joined for five individuals (n=479 observations in 40 infants).

Fractional water excretion (FE_{Water}) was calculated from

$$FE_{Water}=P_{PF-S}/U_{PF-S}$$

or

$$FE_{Water}=P_{Cr}/U_{Cr}\times 1{\cdot}101$$

Excretion and fractional excretion rates calculated from creatinine are accurate for the individual spot urines (but may carry some imprecision because creatinine excretion rate varies up to +32%[13]), and it is not implied that they hold true for other urines passed on the same day. Weight rather than surface area was used because it is physiologically more appropriate in immature infants[11] and more accessible in routine practice. Birth weight was used unless the baby was growing and had regained his birth weight. Factoring by a weight less than birth weight causes false over estimation of renal functions.[11]

Plasma sodium and potassium were measured with ion selective electrodes on a Technicon RA-1000 auto analyser. Coefficient of variation was <1%. Although the electrodes measure concentrations in plasma water, a correction to actual plasma concentration is made automatically. Small differences between the composition of adult and neonatal plasma and the 5–7% of plasma non-water can be ignored (for example in calculating fractional excretion) when we are interested in many-fold differences between subjects in quantities such as fractional sodium excretion. Urine sodium and potassium were measured by flame photometry (Instrumentation Laboratories 913). The coefficient of variation was <1% over range 10–200 mmol/l. Plasma and urine osmolalities were measured by cryoscopy (Gonotec Osmomat 030). The coefficient of variation was <1% over range 50–1000 mosmol/kg.

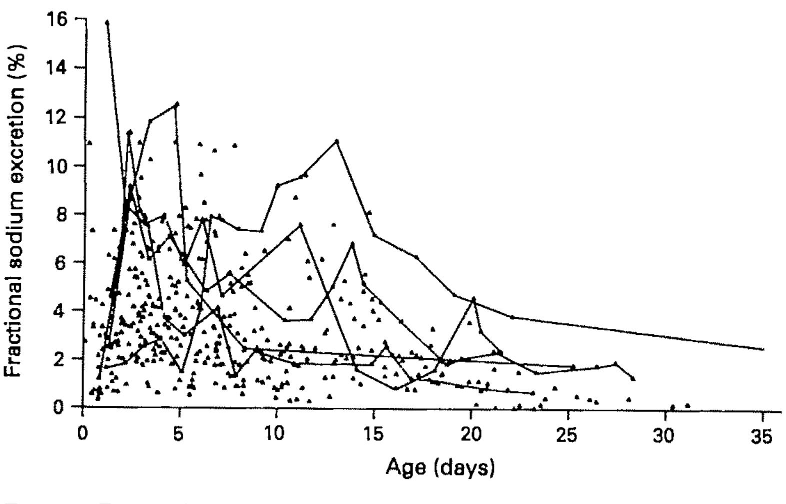

Figure 2 Fractional sodium excretion as a function of postnatal age. Sequential points are joined for five individuals. Of 432 measurements, 120 were made from PF–S infusion experiments and 312 from plasma and urine creatinine.

Results

PLASMA SODIUM

Normal plasma sodium (136–144 mmol/l) was rare especially after age 1 week (fig 1). Hypernatraemia was uncommon and confined to the first week and to infants less than 29 weeks' gestation despite early high sodium excretion. Most infants studied beyond 2 weeks were hyponatraemic, but this was also common in the first week. Many infants had an initial increase in plasma sodium, which was greater in more immature infants and always accompanied by weight loss, reflecting water balance. There was frequently a peak in plasma sodium between 2 and 4 days, occasionally later, followed by a progressive fall, the latter accompanied not by a regaining of weight but by rising or continuing sodium excretion. Late hyponatraemia beyond two weeks was often profound and prolonged (for example fig 5A and C). These features are illustrated in fig 1 by five infants whose sequential points are joined.

SODIUM EXCRETION

There was a wide range of fractional sodium excretion in the first two weeks (fig 2), from zero to 16%. No distinction is made in this and other graphs between creatinine and PF-S derived values, for clarity and because it makes no difference to the message of the paper. There was a postnatal increase in most infants up to a peak which occurred between days 1 and 8, at all gestations from 25–33 weeks, followed usually by a gradual decline although there was considerable fluctuation in some with second peaks. Sodium excretion (mmol/kg/day) had a very similar pattern. The height of the peak in the first week was inversely related to gestational age (fig 3) and in infants less than 28 weeks' gestation the maximum recorded sodium excretion for each baby was 10–22 mmol/kg/day. The regression slope, 1·17 has 95% confidence interval −0·69 to −1·65, $p<0{\cdot}0001$. Total solute (osmolar) excretion varied between 5 and 61 mosmol/kg/day, with higher values seen in the more immature infants.

The magnitude of the early sodium excretion is such that, if continued over several days (the measurements here applied to single voidings only), there is likely to be a cumulative negative sodium balance of up to

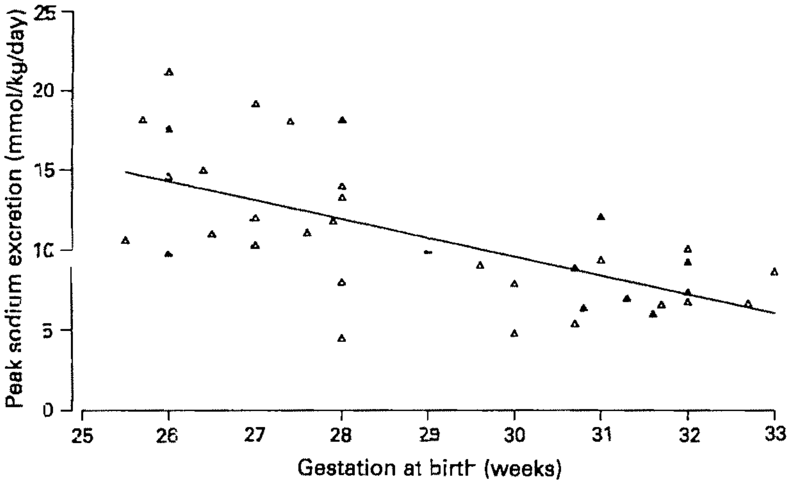

Figure 3 The peak sodium excretion during the first postnatal week as a function of gestation at birth in 38 infants. The least squares linear regression line imposed has the formula. Peak E_{Na} (mmol/kg/day)=44·6−1·17×gestation (weeks)

20 mmol/kg/day, or a fifth of the total body sodium, so it is not surprising that some infants became severely sodium depleted with weight loss of up to 23% of birth weight.

In 10 infants a large increase in sodium excretion occurred after the first week. In one case shown in fig 2 this was in a baby who had had only a modest sodium excretion in the first week and who then had a prolonged excretion of greater than 15 mmol/kg/day in the second week and was still high in the fourth week. This same infant also had early hyponatraemia, weight gain, and delayed water excretion (figs 5A and 6) and a glomerular filtration rate (GFR) low in the normal range. In others a second peak occurred after the initial peak of sodium excretion. In all 10 cases this phenomenon was associated with an acute illness in the child which had the appearance of acute septicaemia. Sepsis was proved in only three infants. In most there was also late worsening of or prolongation of ventilatory failure and ventilation requirements, or the development of symptomatic PDA.

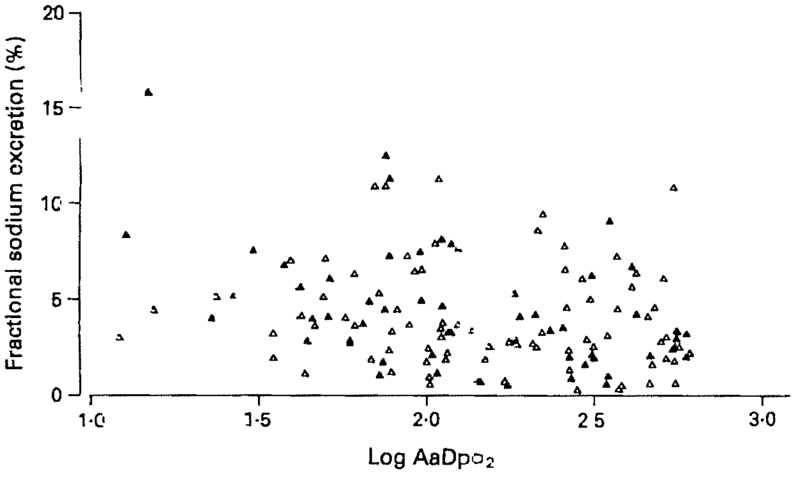

Figure 4 Fractional sodium excretion as a function of AaDpo$_2$ in the first five days (n=140). The abscissa is logarithmic. The regression formula, not shown, is: $FE_{Na}=3·28-1·90\times AaDpo_2$

An initial investigation of the effect of respiratory disease on sodium excretion showed a weak negative relationship between sodium excretion and alveolar-arterial oxygen partial pressure difference (AaDpo$_2$) in the first five days, during which time most infants had a peak in their ventilatory requirement (fig 4). There was no relationship after five days. The regression slope, −1·90 has 95% confidence interval −3·00 to −0·80, $p<0·05$, but the line is not shown because it is not really appropriate when there is a mixture of cross sectional and longitudinal data. This suggests that the early peak in sodium excretion might occur as AaDpo$_2$ is improving.[15] Inspection of individual results is more interesting but shows no standard relationship. In seven infants sodium excretion increased while AaDpo$_2$ was high or still rising, in 14 the peak sodium excretion occurred on the same day as the beginning of a sustained improvement in AaDpo$_2$ and in nine the sodium excretion was already decreasing. Similar results were seen if the arterial:alveolar oxygen partial pressure *ratio* was used instead of AaDpo$_2$.

Inspection of individual sequential results showed no overall tendency for high excretion rates to be associated with higher sodium inputs. Individual excretion and balance are plotted together with plasma sodium concentration, weight and urine flow rate in fig 5 for four infants. In most cases the 'balance' (calculated from the difference between the sodium excretion for the given urine sample and the sodium input at the same time) and excretion varied in parallel and there was only an occasional case, but never in the first week, where an increase in both excretion and negative balance were preceded by an increase in sodium input, for example in fig 5C where hyponatraemia provoked the increased sodium input.

WATER EXCRETION

Fractional water excretion varied widely at all gestations and ages, from 1% to 30% of filtered water (fig 6) or 16 to 350 ml/kg/day. The highest values were in the first two weeks. All results apply to single urine voidings and are not necessarily sustained, and indeed the six individual sequential plots (fig 6) illustrate that water excretion often varied widely from day to day when intravenous water input was constant, and there was no consistent pattern or trend.

Except in two infants, including the infant shown in fig 5A, who had initial weight gain and relative oliguria associated with high ventilation requirement, no relationship could be found between water excretion and oxygenation. Fractional excretion of free water ranged from −5% to +15% of filtered water at all levels of AaDpo$_2$.

Two other babies had initial water retention, but rarely was there prolonged oliguria (<50 ml/kg/day), and never prolonged polyuria (>200 ml/kg/day).

There was no overall relationship between water and sodium excretion. The peak of sodium excretion in the first week was sometimes

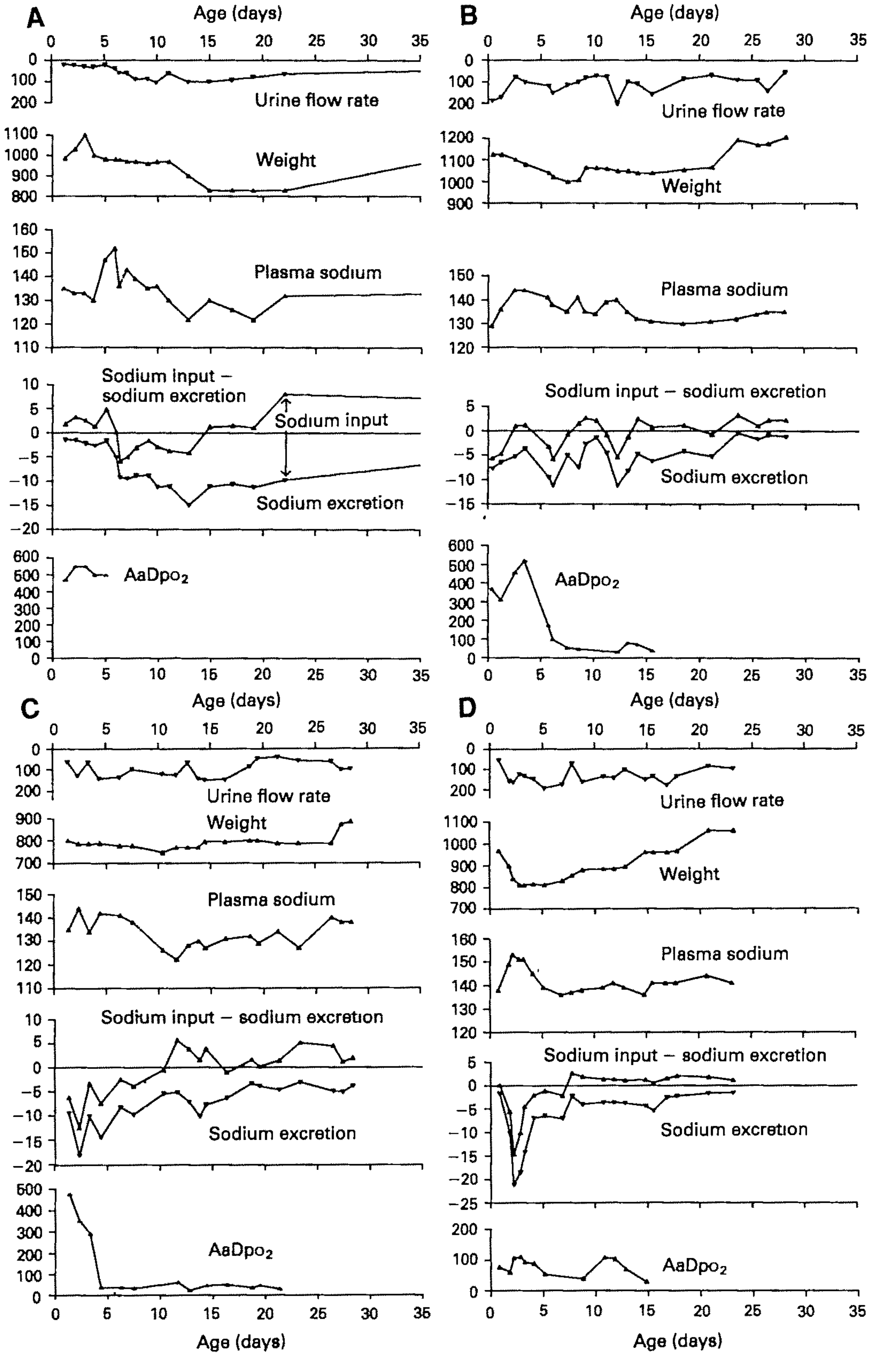

Figure 5 (A)–(D) Details of water excretion (urine flow rate in ml/kg/day), plasma sodium (mmol/l) and sodium excretion (mmol/kg/day), and oxygenation (as AaDpo$_2$ in mm Hg) as a function of postnatal age in four individuals (weight in g).

accompanied by an increasing urine flow rate but this was not usually higher than after the decline in sodium excretion. At later ages, however, a secondary increase in sodium output at times of illness was often accompanied by an increased urine flow, for example fig 5B at age 12 days, suggesting that the increased solute excretion has caused an osmotic diuresis.

PLASMA POTASSIUM

Plasma potassium (fig 7) tended to be high in the first three days, especially in the 20 most immature infants less than 28 weeks' gestation and almost invariably decreased to a nadir at 2 to 6 days, increasing again thereafter illustrated by the three individuals shown. Complications did not occur.

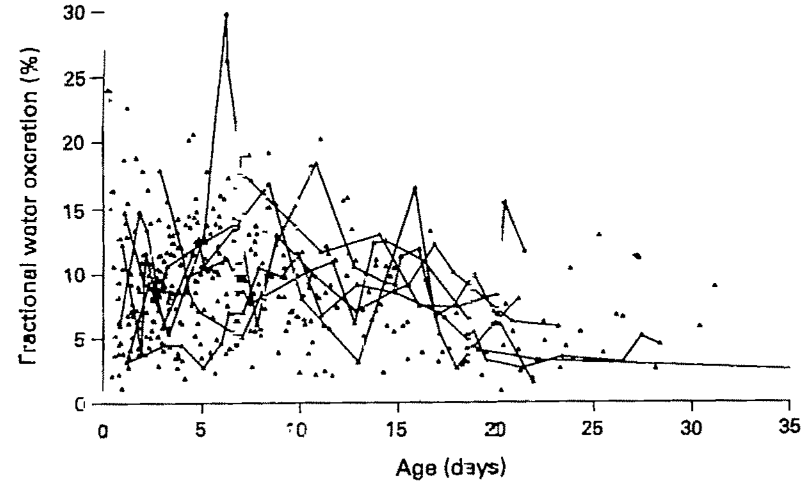

Figure 6 Fractional water excretion as a function of postnatal age Sequential points are joined for six individuals. Of 432 measurements, 120 were made from PF-S infusion experiments and 312 from plasma and urine creatinine.

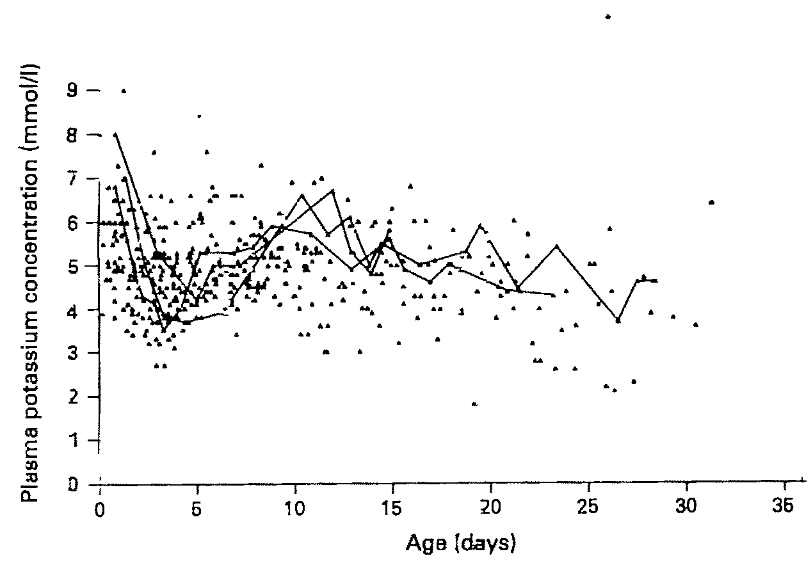

Figure 7 Plasma potassium concentration as a function of postnatal age. Sequential points are joined for three individuals (n=478 observations in 41 infants).

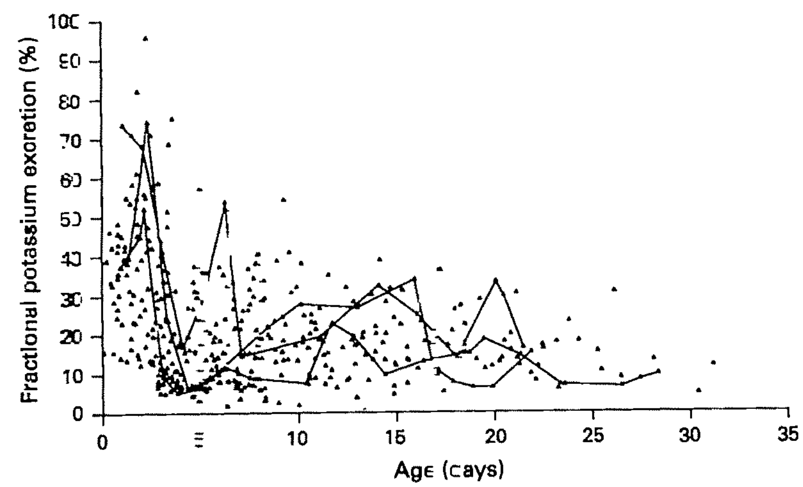

Figure 8 Fractional potassium excretion as a function of postnatal age. Sequential points are joined for three individuals. Of 431 measurements, 120 were made from PF-S infusion experiments and 311 from plasma and urine creatinine

POTASSIUM EXCRETION

Potassium excretion paralleled plasma potassium in the first week with a peak at 1 to 3 days of up to 96% of the filtered load or 1·5 to 5·1 mmol/kg/day (figs 8 and 9). The latter, 5·1 mmol/kg, is more than the total extracellular fluid potassium content and about a 10th of the total body potassium, and potassium was rarely administered in the first two days. Potassium excretion was highest in the most immature. The regression slope in fig 9, –0·283, has 95% confidence interval –0.455 to –0·111, p<0·01. In individual babies there was a common overall pattern of a high potassium excretion in the early postnatal period followed by a rapid decline which is then followed by a later increase to a broad peak in the second week or a little later. Potassium and sodium excretion did not necessarily mirror one another with the nadir of potassium excretion at the same time as the peak sodium excretion. Sometimes both sodium and potassium excretion increased and fell together, in others the sodium excretion remained high and fell after potassium excretion fell.

A scattergram of urine sodium:potassium (Na:K) ratio is similar to sodium excretion (fig 2) suggesting a direct relationship between sodium excretion and the urine Na:K ratio. The correlation is very weak, however, but increased by comparing the logarithms which normalises the distributions of the two quantities (r=0·52 for days 1–5, 95% confidence interval 0·40 to 0·62, p<0·0001, n=177). In any event, normal Na:K ratio in healthy full term infants is about 1 (the ratio of Na:K in breast milk). In very few urine samples was it this low, the majority having a high Na:K ratio up to 70. This might be taken to mean that the high sodium excretion is caused by immaturity of Na:K exchange mechanisms in the distal renal tubule. In this case, one might expect to find an adverse relationship between fractional potassium excretion and fractional sodium excretion. No such relationship was found; in fact there was a direct relationship, especially on days 2 and 3. For example, on day 3 r=0·57, 95% confidence interval 0·32 to 0·75, p=0·0001, n=42.

Potassium excretion correlated strongly with urea excretion on postnatal days 1, 2, and 3 but not thereafter. For example, on day 2 urea and potassium excretion had ranges 1·5–11 and 0·8–4.5 mmol/kg/day respectively, and Pearson's r was 0·75 (95% confidence interval 0·57 to 0·86, p=0·0001, n=35).

Discussion

Many studies have shown high sodium excretion with a rapid postnatal decline and a high incidence of hyponatraemia in immature infants in the first one to three weeks.[1–7 16–20] Higher levels of sodium excretion have been found in the present study matched only by those of one study of very immature sick infants.

Various patterns of postnatal sodium excretion have been found. Whereas it has been previously noted that there is a rapid postnatal

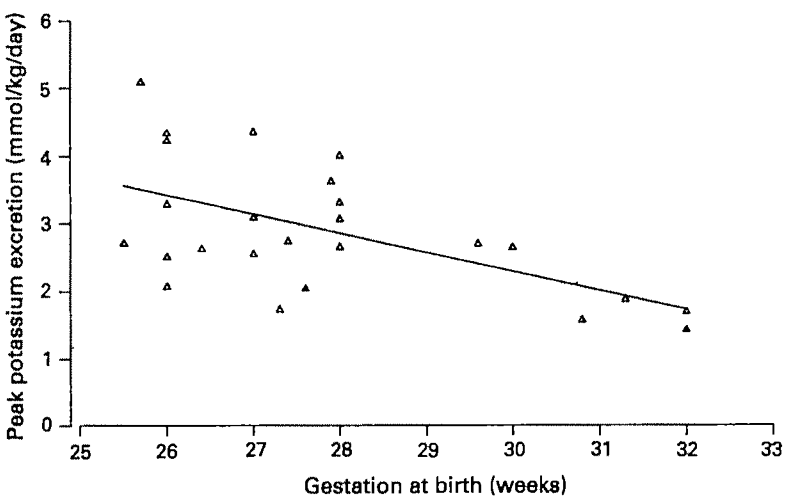

Figure 9 The peak potassium excretion in the first three postnatal days as a function of gestation at birth in 25 infants. The least squares linear regression line has the formula.

decline in the sodium excretion,[2] the frequent initial increase in sodium excretion before the decline, and often a secondary increase, in the present study cannot be attributed to a universal rapid maturation of tubular function. The initial increase might be attributed to the postnatal increase in GFR from low fetal levels, thus flooding the tubules with an increasing filtered load of sodium, but it has also been shown here that GFR reaches its final level by the second day.[11] It would seem that the maturation in terms of ATPase sites can be offset by functional failure, perhaps in the manner of a 'sick cell syndrome' or down regulation of Na/K ATPase. There is no evidence here or in other studies that increased sodium excretion has resulted from higher sodium input (this is generally <5 mmol/kg/day) except in a few instances later than age one week. Further studies are needed to confirm the smoothness of the day to day variation in sodium excretion.

THE CAUSE OF HYPONATRAEMIA

Hyponatraemia may be present at birth reflecting maternal hyponatraemia. The cause of subsequent hyponatraemia in the first week may include sodium wastage or water retention and each have their advocates,[1] although late hyponatraemia is generally agreed to reflect sodium depletion. In the present study sodium depletion was often severe and early and with a frequent fall in plasma sodium without an increase in weight, often after hypernatraemia, this suggests that renal sodium wasting contributes. A third possibility, a generalised cell membrane Na/K ATPase failure with decreased cell membrane gradient and intracellular sodium shift has been dismissed[1] because the plasma sodium is not replaced by another cation. But extracellular and intracellular hypo-osmolality must coexist and this might be caused by either water retention or combined sodium and potassium depletion. The potassium excretion observed here (up to 5 mmol/kg/day) in the first three to four days suggests this is a possibility. Potassium excretion has previously been <2 mmol/kg/day,[2 3 5 20] and well infants are in positive balance.[5 20 21] However, ill infants may be in negative balance.[22] The non-oliguric hyperkalaemia, also observed by others,[3 22–25] is associated with high renal excretion of potassium. This is attributed to a catabolic state because it is associated, as on days 1 to 3 here, with high urea excretion,[3] although the latter continues for much longer in the present study. The potassium wastage may be more specifically the result of deficient or down regulated cellular Na/K ATPase. A further study with accurate potassium balances would help to quantify potassium and sodium losses. Urine collections every four hours with 24 hour moving averages would avoid some of the inaccuracy due to incomplete and variable bladder emptying and occasional incomplete collections.

Healthy preterm infants are able to vary their water excretion according to input.[26] Much of this variation in day-to-day urine volume observed here is not explained. True inappropriate antidiuretic hormone syndrome (SIADH) is probably uncommon in preterm infants,[27] although it has frequently been implicated in causing hyponatraemia in neonates.[6 28] Clinically inapparent volume depletion is common, so it is likely that many cases of alleged SIADH are due to physiologically *appropriate* rather than *inappropriate* antidiuretic hormone secretion. This is a most important distinction to make because in SIADH restriction of water intake is required whereas increased volume input may be required otherwise. Conversely, dehydration is not necessarily implied by a combination of high plasma urea and low urine flow.[13]

A possible reason for some occasions of high urine flow may be a high osmolar excretion rate; for example, if the maximum urine osmolality is 600 and the osmolar excretion rate is as high as 60 mosmol/kg/day, then a urine volume of at least 100 ml/kg/day is required in order to excrete this obligatory solute. An obligatory water, as well as solute, loss may therefore be occurring, especially when urine osmolality is not maximal.

THE NATURE OF THE SODIUM WASTAGE

The sodium depletion may be attributed to failure of proximal tubule reabsorption.[5] Although the distal tubule fails to compensate[29 30] distal reabsorption is probably relatively intact.[31] Various animal models, mainly rat and rabbit, show a slow postnatal increase in the number of Na/K ATPase sites after birth.[32–37] This is preceded by a slow increase in the sodium permeability of individual cells and can be inhibited by chronic administration of amiloride suggesting that the development of the pump is stimulated by sodium substrate itself. This may explain the apparent acceleration of renal tubular maturation.[34–37] Marsupial pouch young, born very immature, may normally have low plasma sodium concentrations rising throughout pouch life from about 110 mmol/l to 140 mmol/l (G Wilkes, S Thomas, P Janssens, B H Wilkins, unpublished observations), but they are unlikely to be chronically sodium depleted because they grow very fast. In the premature infant sodium depletion probably matters more than hyponatraemia itself in terms of subsequent growth.[1] The fact that early and transitional milk and the milk of mothers of prematures (and marsupial milk) contains higher sodium,[38-41] and that sodium supplementation promotes a more stable plasma sodium, sodium repletion and growth,[5 8 42] are further evidence that sodium depletion is not the best state of affairs for preterm infants

Those who advocate that this may be a *physiological* adaptation to the demands of the circulatory changes after birth[7 9 17 43 44] ignore the high sodium excretion continuing after the extra cellular fluid contraction and the late increases in sodium excretion observed, presumably caused by down regulated Na/K ATPase. Sodium and water restriction together may not lead to hyponatraemia[10] but will lead to volume contraction and delayed growth.[1] Sodium homoeostasis in the newborn is geared towards sodium conservation not excretion, and an expanding extracellular volume. PDA, sometimes attributed to volume[45] overload and failure to contract extra cellular space, was seen in this study in infants who lost 20% of birth weight as well as in those who lost none.

Glomerulotubular balance may well be deficient[2 27] but in immature infants there is a major failure of sodium reabsorption in the proximal tubule at a degree at which glomerulotubular balance will not normally operate. This is a *fine control* mechanism which prevents wide fluctuations in tubular fluid delivery to the distal tubule due to *small* changes in GFR or proximal tubular fluid handling.

NATRIURESIS AND RESPIRATORY DISEASE

It is speculated that atrial natriuretic peptide (ANP) plays a part in the isotonic contraction of extracellular fluid in mature and immature newborns.[15 46-48] Hormones have not been measured in the present study but in several studies mean ANP concentrations are very much higher in preterm infants and may be contemporaneous with natriuresis, but not always.[43 46 49 50] This has led to the speculation that improving pulmonary perfusion causes ANP release by left atrial distension thereby causing the natriuresis associated with improving respiratory function.[15 50]

There are conflicting reports concerning the effect of respiratory disease. An increased fractional sodium excretion has been observed,[51 52] which suggests that respiratory disease impairs tubular function. Others found no influence on the sodium excretion.[17] There is usually a diuretic phase before, after, or during recovery from respiratory disease which may represent a delayed contraction of extracellular water space.[15 53 54] ANP is a hormone whose function is not just natriuresis but to protect against volume overload. Hypoxia and high pulmonary vascular resistance are other, non-physiological stimuli. Just as the high aldosterone concentration does not necessarily mean that it is effecting a normal physiological response,[5 20] so also it would be incorrect to assume that high ANP levels are entirely physiological.

IMPLICATIONS FOR TREATMENT

We do not know in individuals how much of the early and late sodium loss should be replaced nor to what extent the variable postnatal weight loss is a necessary adaptation to the change in circulatory anatomy. There is unlikely to be an ideal weight loss for all infants. Advocators of sodium and water restriction,[9 10] and therefore volume depletion, say that water excess is a disadvantage as a rule. Although sodium supplementation to 5 mmol/kg/day improves weight gain in some infants,[8] we now need a trial to compare a policy of volume depletion with one of volume repletion, and to determine whether early sodium replacement in sick very low birthweight infants makes any difference to weight gain, to the incidence of PDA and other complications, to duration of hospitalisation or to neurodevelopmental outcome. A three armed study would be needed comparing (1) low water input and sodium supplementation only according to evidence of sodium depletion,[10] (2) high water input with elective early sodium supplementation to 3, 4, or 5 mmol/kg/day,[8] and (3) high water input with prospective sodium replacement according to measured losses.

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Renal function in sick very low birthweight infants: 4. Glucose excretion

Barry H Wilkins

Abstract

Renal glucose excretion was measured on 239 occasions in a sample of 36 infants of 25·5–33 weeks' gestation, birth weight 720–2000 g, between the ages of 0·5 and 32 days. Glucose was invariably present in urine from the first day. Fractional glucose excretion varied widely from 0·1% to 90% of filtered glucose and glucose excretion rate was up to 15·5 mmol/kg/day and was higher in the most immature infants, especially below 28 weeks' gestation. The highest values were in association with hyperglycaemia between 5 and 15 days but there was no consistent plasma glucose threshold with frequent glucose spillage at normal blood glucose concentrations. There was some correlation with sodium excretion in the first week suggesting that in the absence of hyperglycaemia with a normal filtered glucose load, glucose excretion is caused by proximal tubular immaturity.

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The clinical management of sick preterm infants includes attention to the daily prescribing of nutrition and maintenance of normal plasma glucose concentration. Urine is frequently tested for the presence of glucose and it is alleged that glucosuria may cause osmotic diuresis and dehydration,[1] although there is surprisingly little evidence that this is a real danger. It has long been known that premature infants have a lower tubular reabsorption maximum[2–11] and that glucosuria can be exacerbated by increasing plasma glucose concentration.[3] This has not been quantified in the sickest and most immature infants in whom glucosuria is observed at normal plasma glucose concentrations.

The purpose of the present investigation was (1) to quantify glucose excretion in sick infants less than 33 weeks' gestation at various ages; (2) to determine whether this may represent significant wastage of glucose energy, and (3) to investigate whether osmotic diuresis is a real possibility.

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Patients and methods

This study was part of a wider study of glomerular and tubular function in very low birthweight infants.[12] Thirty six were chosen who could be studied in the first postnatal week, and later if possible. Gestation at birth was 25·5–33 weeks, birth weight 720–2000 g. Further clinical, experimental, and laboratory details are given in Part 1.[12]

Glomerular filtration rate (GFR), plasma glucose concentration, and renal glucose excretion were measured sequentially in 36 infants up to age 3–33 days. Plasma glucose was only measured when plasma was separated from heparinised blood within one hour of collection. GFR and urine flow rate were measured by a continuous infusion Polyfructosan-S (PF-S, Laevosan-Gesellschaft) clearance method.[12]

When PF-S was not being infused urine flow rate was calculated from:

Urine flow rate=creatinine excretion rate/urine creatinine concentration

and GFR from:

GFR=creatinine excretion rate/plasma creatinine concentration

where creatinine excretion rate is that measured in that baby in nearby PF-S infusion experiments.[13] Filtered glucose was calculated from:

Filtered glucose=GFR×plasma glucose concentration

Fractional glucose excretion ($FE_{Glucose}$) was calculated from

$$FE_{Glucose}=U_{Glucose}/P_{Glucose}\times P_{PF\text{-}S}/U_{PF\text{-}S}$$

or

$$FE_{Glucose}=U_{Glucose}/P_{Glucose}\times P_{Cr}/U_{Cr}\times 1{\cdot}101$$

where 1·101 is the mean ratio between PF-S and creatinine (Cr) clearance.[14] Glucose was measured in undiluted urine, plasma, or aqueous standards by a glucose oxidase/peroxidase photometric method on an Instrumentation Laboratories discrete semiautomated glucose analyser. There were no interfering substances and the coefficient of variation was 2% at 1 mmol/l and <1·0% at 10 mmol/l.

Results

Plasma glucose concentration varied from 1·2–13·8 mmol/l in 262 samples. Only three measurements were <2 mmol/l and 15 >10 mmol/l. Glucose was invariably detected in urine at all ages, 1 to 101 mmol/l in 329 samples. In only 19 was the glucose concentration >14 mmol/l (¼%), in eight >28 mmol/l (½%), and one sample had glucose >55 mmol/l (1%). The great majority of samples had very low glucose concentrations measurable only by laboratory methods and not detectable by ward dipstick testing.

The four graphs contain a mixture of cross sectional and longitudinal data. Fractional glucose excretion ($FE_{Glucose}$, fig 1) varied from

0·1% to 90% of filtered glucose. Values up to 5% occurred from the first day in all gestations but most of the highest values, >10%, are seen from age 5 to 15 days and in the most immature infants below 28 weeks' gestation at birth (fig 2). Glucose excretion rate (mmol/kg/day) had a similar pattern to $FE_{Glucose}$ and varied from 0·01 to 15·5 mmol/kg/day in 239 measurements, but was >0·5 mmol/kg/day in only 50 and >1 mmol/kg/day in 30, almost all in infants less than 28 weeks' gestation.

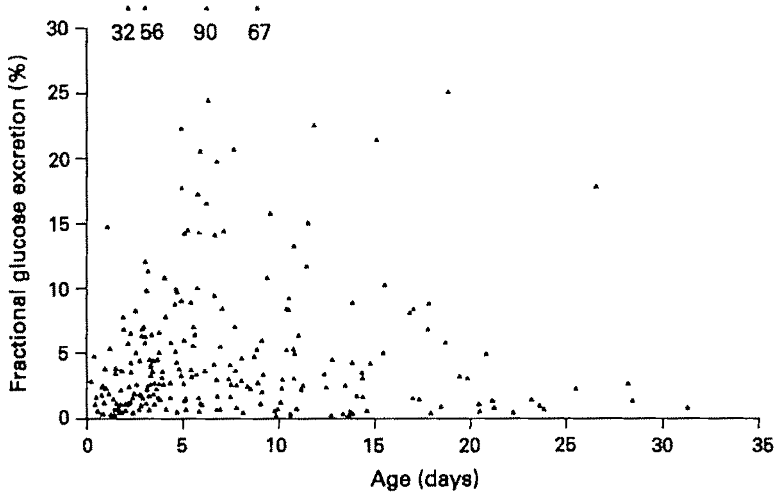

Figure 1 Fractional glucose excretion as a function of postnatal age on 239 occasions in 36 infants (82 measurements were made from PF-S infusion experiments and 157 from plasma and urine creatinine and glucose).

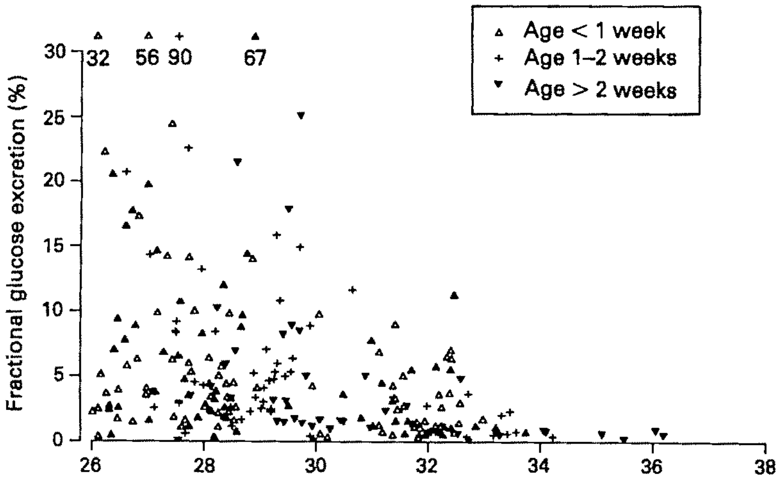

Figure 2 Fractional glucose excretion as a function of postconceptional age in three age groups (n=239, 143 at <1 week, 59 at 1–2 weeks, 37 at >2 weeks).

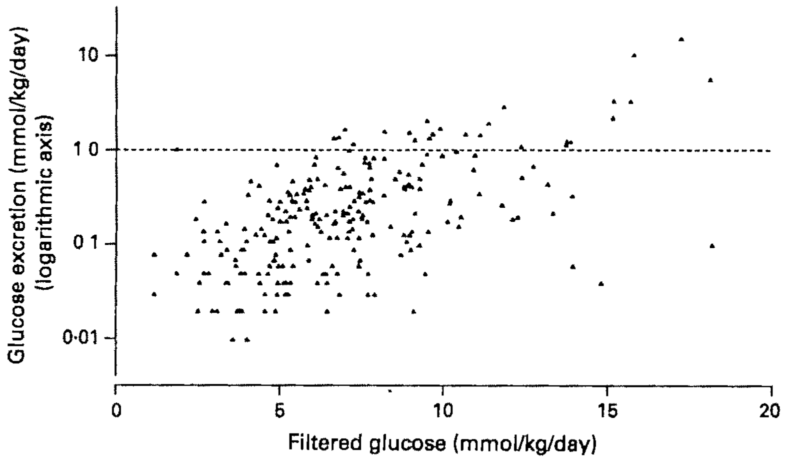

Figure 3 Glucose excretion rate as a function of glucose filtered load (n=239). On 101 occasions filtered glucose was calculated from PF-S clearance experiments, and on 138 from creatinine.

There was no consistent threshold of glucose filtration rate or plasma glucose concentration above which glucose appears in the urine (fig 3). The scattergram is similar whether the abscissa is plasma glucose or filtered glucose, or whether the ordinate is glucose excretion or fractional glucose excretion. Glucose excretion >0·5 mmol/kg/day occurred with normal plasma glucose but the highest values, >2 mmol/kg/day, only occurred with hyperglycaemia. In the four occasions when excreted glucose was >4 mmol/kg/day this represents considerable glucose wastage, approximately 15% to 35% of administered glucose, but such occasions were exceptional.

The relationship between glucose excretion and sodium (Na) excretion was complex (fig 4). The highest values of both occurred in the sickest and most immature infants. Low values of glucose excretion occurred at all levels of sodium excretion but the maximum $FE_{Glucose}$ increased from negligible to 10% as FE_{Na} increased from zero to 2%. This is not surprising in view of the common proximal tubular reabsorptive mechanism for sodium and glucose, but the highest values of glucose excretion were associated with hyperglycaemia and increased filtered load at age 5–15 days, whereas filtered sodium load is relatively constant between babies and sodium excretion peaked in the first week.[15]

Low levels of glucose excretion occurred at all levels of alveolar-arterial oxygen partial pressure difference ($AaDpo_2$) or arterial: alveolar gradient ($aApo_2$ ratio). All but two of the high levels of glucose excretion ($FE_{Glucose}$ >10%, glucose excretion >0·5 mmol/kg/day) occurred when $AaDpo_2$ was <100 mm Hg (13·3 kPa) or aApo2 ratio >0·3, and almost always during the recovery period after severe respiratory illness.

The few instances of high urine glucose concentration (>28 mmol/l, 0·25%) and high glucose excretion (>3mmol/kg/day) were always isolated and not repeated in any baby. However, prolonged glucose excretion >1 mmol/kg/day occurred in five infants <28 weeks' gestation for periods of three to eight days when plasma glucose concentration was 5–13 mmol/l and urine glucose 6–101 mmol/l. Most of these occasions were associated with a secondary illness, usually with signs suggestive of necrotising enterocolitis or acute sepsis which was proved in three cases. Sometimes sodium excretion secondarily increased as well but not all instances of sepsis were accompanied by hyperglycaemia and/or high glucose excretion.

No obvious osmotic diuresis was observed in association with high urine glucose but it cannot be excluded because urine flow rate can vary widely from day to day irrespective of glucose excretion.[15] The table details indices

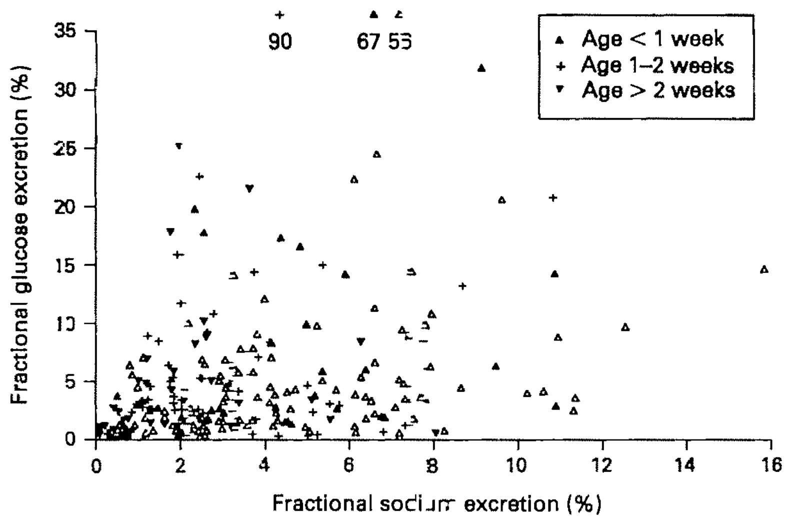

Figure 4 Fractional glucose excretion as a function of sodium excretion in three age groups.

Indices for the eight urine samples in eight patients with the highest urine glucose concentrations

Urine glucose (mmol/l)	*Plasma glucose (mmol/l)*	*Urine osmolality (mosmol/l)*	*Urine sodium (mmol/l)*	*Urine urea (mmol/l)*	*Urine flow rate (ml/kg/day)*	*Glucose excretion (mmol/kg/day)*	*Total osmolar excretion (mosmol/kg/day)*
101	13·8	327	42	62	153	15·5	50
52	13	192	56	19	202	10·5	39
45	13·4	482	142	86	129	5·8	62
41	8	350	99	68	43	1·8	11
40	13	195	43	10	88	3·5	17
32	10	140	70	20	106	3·4	15
29	7	123	16	19	245	7·1	30
29	13	310	54	26	42	1·2	13

for the eight occasions when urine glucose concentration was greater than 28 mmol/l. Glucose accounted for up to 31% of excreted solute, the rest being mainly sodium chloride and urea. Urine osmolality was always well within the normal range.

Discussion

The normal, mature kidney excretes only very small quantities of glucose, the fractional excretion by the renal tubule being close to 0%.[16 17] Glucose only appears in the urine when the plasma glucose concentration increases above the threshold for saturation of the tubular transport mechanism.[3 4 6 9] A low glucose threshold is often assumed in the preterm, but in the present study it is very variable even without hyperglycaemia. Although glucose excretion was low in the majority of samples tested, significant glucose spillage can occur when the plasma glucose concentration is normal and urine glucose concentration is only ¼–½%, which would normally be ignored in clinical practice. This may represent up to 35% of the glucose energy administered to the infant (6 mg/kg/min glucose input=48 mmol/kg/day) and so exceptionally it may represent significant energy wastage. This is nevertheless negligible in the majority of samples tested.

Although glucose reabsorption in the proximal tubule depends on Na/K ATPase this failure to conserve glucose does not parallel sodium excretion. Failure of glucose conservation implies proximal rather than distal tubular dysfunction, whereas failure of sodium reabsorption may occur in all parts of the tubule which may account for some instances of high FE_{Na} but low $FE_{Glucose}$. Developmental studies in the rabbit have shown that glucose and bicarbonate reabsorption mature before sodium.[8 18] It is likely that in the absence of hyperglycaemia failure of glucose reabsorption is caused by failure of sodium reabsorption in the proximal tubule and depends on the degree of tubular immaturity. It cannot be due to volume expansion[19] because most of these infants are volume contracted.

The present results for glucose excretion are higher than previously reported in less ill and more mature infants[4–7 9] but similar to those of one previous study which reported up to 45% $FE_{Glucose}$ in sick ventilated newborns.[20] They also reported no difference between stable and unstable ventilated infants (no measure of respiratory severity was given) but much lower levels in unventilated infants. These and the present results suggest that sickness, such as sepsis but not respiratory disease, as well as immaturity contribute to failure of tubular glucose reabsorption.

High levels of excretion of filtered solute that the tubules cannot reabsorb may cause an obligatory increase in flow of filtered water through the nephron, an osmotic diuresis. Either exogenously administered osmotic agents, which increase plasma osmolality and therefore the filtered osmolar load, or the failure of the tubule to reabsorb a specific solute such as glucose, may have this effect. The presence of unreabsorbable osmoles such as glucose in the proximal tubule inhibits the reabsorption of water which normally follows the active sodium chloride reabsorption.[21] In turn this leads to an increased flow rate through the tubule and a decrease in the sodium chloride concentration in the tubular fluid. These effects combine to reduce or even eliminate the medullary concentration gradient. Water reabsorption in the collecting duct may therefore be minimal even in the presence of a high concentration of antidiuretic hormone. Under conditions of maximal osmotic diuresis the urine osmolality approaches that of plasma whether there is pre-existing dehydration or pre-existing water diuresis. An osmotic diuresis caused by an increased excretion of osmoles is usually associated with a change in urine osmolality away from the extremes. Therefore osmotic diuresis cannot be excluded on the basis of normal urine osmolality despite a suggestion otherwise.[20]

It is possible, therefore, that on the rare occasions when glucose makes a significant contribution to an abnormally high total osmolar excretion it may cause an obligatory increase in water excretion.

In clinical practice this will not matter so long as clinicians pay attention to adjusting water input according to estimated water excretion (from random urine creatinine[13]) and weight change. Moreover, there is little value in measuring urine glucose; it is more important to maintain normal plasma glucose concentration by adjusting glucose input.

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Simultaneous measurement of preductal and postductal oxygen saturation by pulse oximetry in hyaline membrane disease

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Abstract

Preductal and postductal oxygen saturation were compared in 20 ventilated preterm infants with hyaline membrane disease to establish the frequency of right to left shunting and to assess the accuracy of postductus arteriosus blood gas sampling. One hundred and thirty eight comparisons were made and the frequency of right to left shunting was 17% (95% confidence interval 12 to 25%). Shunting episodes with possible preductal hyperoxia occurred far less commonly on a maximum of 5% of occasions. The findings in infants under 1000 g and of 24–28 weeks' gestation were not significantly different from larger or more mature infants. Shunting occurred significantly more frequently in very ill infants who subsequently died as a result of respiratory disease.

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Ventilated premature infants require close monitoring of oxygenation. This is currently carried out by a variety of methods including blood gas analysis from different sites, transcutaneous monitoring of oxygen tension (Po_2) and oxygen saturation monitoring. With the exception of arterial blood samples taken from the right arm and saturation probes positioned at this site all these methods rely on sampling from areas perfused by postductus arteriosus blood flow. In the first day of life bidirectional shunting through the ductus may occur and this is often proposed as an explanation for a poor Po_2. Such shunting has been clearly demonstrated in the past by invasive methods but mainly in relatively large babies who were predominantly not ventilated.[1 2] If significant bidirectional or right to left shunting is occurring then blood perfusing the right subclavian and carotid arteries could have a substantially higher oxygen content than that being measured. This is obviously of greatest relevance in the smallest and most premature infants requiring ventilatory support and at greater risk of retinopathy of prematurity. With the exception of one previous study[3] the problem of shunting in such infants has been largely ignored. Thus it is important to make a comparison of oxygenation at a preductal and postductal level in these small infants. The easiest and least invasive method of doing this is by the use of pulse oximeters; this method has been used previously to document right to left shunting in the first minutes of life during resuscitation of newborn infants.[4]

The aim of this study was to identify the frequency of right to left ductal shunting at the time when postductal arterial blood gas samples are obtained and to assess the reliability of such samples.

Patients and methods

Infants of 32 weeks' gestation and under were recruited to the study if they required early ventilation for hyaline membrane disease and had either an umbilical arterial catheter or a peripheral arterial line sited in a lower limb artery. During the first 36 hours of life recordings of oxygen saturation were made when arterial blood gases were checked. Immediately before obtaining a blood sample Ohmeda Biox 3700 pulse oximeters were attached to the right arm and either foot. To avoid movement artefact the pulse waveform was observed until there was a strong steady signal with a pulse rate that matched that on the cardiac monitor. It usually required five minutes for the infant to settle and the signals to stabilise. When there was a reliable signal from each monitor a blood sample was taken and the saturation readings recorded. All samples were obtained and recordings made by a single observer (PDM). The oximeter probes were shielded from extraneous light to avoid interference.

In the initial studies (first 10 patients and 76 measurements) the monitor positions were switched whenever a saturation discrepancy was noted. As this consistently gave the same result this practice was abandoned in the later studies to minimise disturbance to the babies. A saturation in the right arm of at least 3% above the lower limb was taken to indicate right to left ductal shunting. Such a difference represents a right to left ductal shunt of approximately 10% of the postductal blood flow assuming normal mixed venous saturation.[5]

Results

Twenty infants were enrolled in the study with a mean birth weight of 1095 g (range 660–1750). The mean gestation was 27·7 weeks (range 24–32 weeks). All were ventilated for hyaline membrane disease within six hours of birth. A total of 138 comparisons were made ranging from four to 11 for each infant (mean 6·9 for each infant). Eight of the

Table 1 Upper limits of PaO_2 at given lower limb saturation

Lower limb postductal saturation (%)	No of infants	Postductal PaO_2 (kPa)	
		Mean	Mean+1 645 SD
99–100	4	15·1	18 0
97–98	12	10 9	16 4
95–96	20	8·8	13 2
93–94	26	8 8	11 5
91–92	27	7 8	10 4
89–90	16	7 9	10 2
87–88	12	6·9	8 9
85–86	7	6 3	7 3
81–84	6	6 0	7 5
70–80	4	5 6	6 7
<70	4		

20 infants weighed under 1000 g at birth and 11 of the 20 were born at 24–28 weeks' gestation. An initial comparison was made of arterial oxygen tension (PaO_2) and postductal saturation to identify the upper limits for PaO_2 at each saturation level. Table 1 gives the limits (mean+(1·645 SD)) below which 95% of values fall. From this it was concluded that saturations above the 93–94% bracket could be associated with an increased PaO_2 value above 11·5 kPa (87·4 mm Hg). Preductal saturations greater or equal to 93% in the presence of a saturation difference of at least 3% were subsequently viewed as potential preductal hyperoxia.

Table 2 shows the discrepancies between the right hand and foot saturation readings. On 32 occasions the foot reading was higher than the right arm by 1 or 2%; these 'impossible' recordings presumably reflect the resolution and accuracy of the monitors. The fact that the foot saturation was never more than 2% above the right hand reinforces our decision to define a shunt as a foot saturation of at least 3% below that in the right hand. Right to left shunting was identified on at least one occasion in half the infants. Shunting episodes where the preductal saturation was ≥93% (representing possible preductal hyperoxia) occurred in five of the 20 infants.

Examining the infants weighing <1000 g or of 24–28 weeks' gestation showed that neither group differed significantly from the heavier or more mature infants (Fisher's test; see table 3).

Of a total of 138 measurements performed on these 20 infants right to left ductal shunting was shown 24 times: 17·4% of occasions (95% confidence interval 12 to 25%). Shunting with preductal saturation ≥93% occurred on seven occasions.

Table 2 Saturation discrepancies among measurements made

Difference in saturation between foot and right arm	No of measurements (n=138)
+3 or greater	0
+2	13
+1	19
0	47
−1	30
−2	5
−3	6
−4	5
−5	3
−6	3
−7	1
−8	1
−9	2
−12	2
−25	1

Table 3 Frequency of right to left shunt among infants studied

Characteristic of infant	No of infants	No (%) with right to left shunt	No (%) with preductal oxygen saturation ≥93%
Gestation (weeks)			
24–28	11	6 (55)	2
29–32	9	4 (44)	3
Weight (g)			
<1000	8	4 (50)	2
≥1000	12	6 (50)	3
All infants	20	10 (50)	5 (25)

Table 4 Frequency of right to left shunt among measurements made

Characteristic of infant	No of measurements	No (%) with right to left shunt	No (%) with preductal oxygen saturation ≥93%
Gestation (weeks)			
24–28	68	15 (22)	2
29–32	70	9 (13)	5
Weight (g)			
<1000	46	8 (17 4)	2
≥1000	92	16 (17 4)	5
All infants	138	24 (17 4)	7 (5·1)
95% Confidence interval		11 5 to 24 8%	3 4 to 10 2%

Examining measurements in infants of <1000 g or gestation 24–28 weeks showed no significant difference in the frequency of shunting episodes nor of hyperoxic shunts compared with the measurements in the heavier or more mature infants (table 4).

Three of the infants died due to severe hyaline membrane disease complicated by pulmonary interstitial emphysema. Shunting was seen in all three infants who died compared with seven of the 17 who survived. There was a highly significant increased frequency of shunting in those who died occurring in 11 of 16 measurements compared with 13 of 122 measurements in those who survived ($p=2{\cdot}3\times10^{-6}$; Fisher's test). One infant died early at 11 hours after birth with evidence of shunting on four of four occasions, but even if his data are excluded the increased frequency remains highly significant ($p=5{\cdot}82\times10^{-4}$). The other two infants survived throughout the study and developed shunting later in the 36 hour period as their disease progressed. Only one of the 11 episodes was associated with possible preductal hyperoxaemia.

The most marked example of shunting in an infant who survived was a 1004 g, 25 week gestation infant. She had evidence of right to left ductal shunting on four of seven comparisons with saturation differences of 5, 5, 3, and 6%; her highest preductal saturation with evidence of right to left ductal shunt was 92%.

Discussion

These results confirm that right to left ductal shunting is common in the first 36 hours of life in these premature infants. The primary aim of this study was to identify the extent to which postductal arterial blood gas interpretation can be distorted by right to left ductal shunting rather than to document how long such shunts lasted. Such distortion could be occurring in up to 25% of blood gas samples (upper limit of 95% confidence interval). Preductal hyperoxaemia occurs much less often, however, and does not appear to be a major problem. Our level of identifying such preductal hyperoxaemia was chosen as a worst possible scenario and is likely to be an overestimate. A substantial number of the shunting episodes occurred in the most severely ill babies who subsequently died of their respiratory disease. We have concentrated on identifying right to left ductal shunting in the more immature infants in whom the dangers of hyperoxaemia are greatest. Neither infants under 1000 g nor those of 24–28 weeks' gestation differed significantly in their incidence of shunting from the rest of the study sample.

Concern has previously been raised about the possibility of large right to left shunts occurring in premature babies.[5] Roberton and Dahlenburg studied this problem in 21 infants with hyaline membrane disease by examining paired preductal and postductal arterial gases.[1] Nine of their infants had discrepancies in PaO_2 at times when the postductal PaO_2 was within the normal range; only one of these infants was of less than 32 weeks' gestation. Eight of their 21 infants were ventilated at some time but only three appear to have been ventilated during the study period. It is thus difficult to apply their data to the smaller, less mature ventilated infant.

Pearlman and Maisels examined preductal and postductal transcutaneous PO_2.[3] Most of their infants were ventilated but not all. Their results were reassuring, concluding that clinically important differences between preductal and postductal PO_2 were infrequent and short lived. Their study enrolled relatively mature infants up to 35 weeks of gestation, however, and only included three infants under 1000 g.

Our results are consistent with those from previous studies but provide additional data relating to the more premature and smaller infants. We are reassured that postductal arterial gas measurements are a safe means of monitoring oxygenation in these infants. Placement of twin oximeter probes on the right hand and a foot appears to be an effective method of identifying right to left ductal shunting. Although preductal hyperoxaemia resulting from such shunts is uncommon, it is reasonable to preferentially use the right hand if using a pulse oximeter in ventilated premature infants.

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Effect of patency of the ductus arteriosus on blood pressure in very preterm infants

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Abstract

Forty one preterm infants (birth weight <1500 g) were studied by daily Doppler echocardiography for the first week of life to examine the effect of a haemodynamically significant ductus arteriosus (HSDA) on systemic blood pressure. Hourly records of blood pressure were averaged for each infant to produce a 24 hour mean value and the infants were then allocated to groups according to whether, by echocardiographic criteria, there was a HSDA on that day.

In infants from 1000 to 1500 g the differences in all parameters of blood pressure between those with and without a HSDA were not significant. In infants <1000 g the mean blood pressure was significantly less in the infants with a HSDA throughout the first week of life. Systolic blood pressure was reduced by as much as diastolic blood pressure and as a result the pulse pressure did not differ. Infants <1000 g with a HSDA were given more plasma and a greater number received inotropic support. Gestational age, respiratory disease severity, and complication rates did not differ between those with and without a HSDA.

The possibility of a clinically silent HSDA should be considered before large amounts of plasma volume expanders are given to treat hypotension in infants <1000 g.

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The classical description in many textbooks of neonatology of the effect of shunting through a haemodynamically significant ductus arteriosus (HSDA) on blood pressure is that it leads to a decrease in diastolic blood pressure causing a widened pulse pressure and hence bounding peripheral pulses.[1] Although this is true in older infants and children there is little published work to support this statement in preterm infants, particularly in the first week after birth when diagnosis is so important.

During a Doppler echocardiographic study of ductal shunting in preterm infants[2] we became aware that large, often clinically silent, ductal shunts seemed to be associated with a more global reduction in systemic blood pressure and that some of the smaller infants seemed to be requiring more medical support to maintain an acceptable blood pressure. These observations agreed with the findings of Ratner *et al* who showed that a HSDA was associated with a reduction in systolic and diastolic blood pressure.[3] Ratner *et al* used the left atrial aortic root ratio as an isolated measurement to assess ductal status and some indirect blood pressure measurements,[3] both of which could have limited the accuracy of their observations. We decided to re-examine this issue in preterm infants with a birth weight <1500 g using direct two dimensional and Doppler echocardiographic diagnosis and only measurements of blood pressure made through an intra-arterial catheter.

Subjects and methods

All subjects were studied with an ATL Ultramark 4 scanner with range gated pulsed Doppler. Cross sectional imaging was performed with a 7·5 MHz transducer incorporating a 5 MHz Doppler crystal. Infants, where possible, had daily echocardiographic examinations for the first week of life (first five days in infants, birth weight >1000 g) with the first study within 24 hours of birth. Occasional days were missed for technical or clinical reasons; blood pressure data from these days were not included in the analysis. Normal cardiac anatomy was confirmed then the ductus was imaged from the high left parasternal position, the Doppler sample volume was placed in the pulmonary end of the duct, and the flow pattern recorded. The duct was classified as 'closed' when patency could not be imaged and no flow could be detected on a pulsed Doppler search of the pulmonary end of the duct. It was classified as 'restricting' when local restriction or no patency could be imaged but a Doppler flow of variable signal intensity was recorded, and as 'widely patent' when unrestricting patency was imaged and a strong Doppler flow signal recorded. When ductal patency was established, the left atrial to aortic root ratio (LA:Ao) was measured according to previously reported criteria[4] as a quantitative measure of the degree of left to right shunt. A mean of three measurements was taken.

Hourly measurements of systolic blood pressure, diastolic blood pressure, and mean blood pressure were recorded from the time of insertion of the intra-arterial catheter. Umbilical lines were size 3·5 FG Argyle catheters; peripheral arterial catheters were 24GA Quik-Cath (R) cannulae. The catheter site was postductal (umbilical, left radial, or posterior tibial) in 17 of the 20 infants who developed a HSDA and in 19 of the 21 infants who did not; the other catheters were preductal in the right radial artery. All catheters were connected for continuous arterial pressure monitoring to a Viggo-Spectramed (R) Quartz transducer placed at mid-thoracic level, which was in turn connected to a Hewlett-Packard HP78834A multichannel monitor. All systems were routinely recalibrated according to the manufacturers' recommended protocol at least once every 24 hours. Pulse pressure was calculated from the difference between the systolic blood pressure and the diastolic blood pressure. The signal was regarded as damped when the pulse pressure was less than 12 mm Hg; only the mean blood pressure was used from these recordings. For each infant the hourly measurements of systolic blood pressure, diastolic blood pressure, and mean blood pressure were averaged over each day to produce 24 hour means for each parameter. For the purpose of this study we defined HSDA as a widely patent duct from which a strong Doppler signal could be recorded where the LA:Ao ratio was greater than or equal to 1·5. The 24 hour means for blood pressure parameters were allocated to groups according to whether the duct fulfilled these criteria within that 24 hour period.

Forty one preterm infants were studied over two six month periods which ended in February 1990 and August 1991 respectively. All infants <1500 g who had satisfactory intra-arterial blood pressure monitoring were recruited during these periods. The only infants not included were born when the investigator with the echocardiographic skills (NE) was on leave. The results were analysed in two different weight groups: <1000 g (n=16) and 1000–1500 g (n=25). Eight of the <1000 g and 12 of the >1000 g infants developed a HSDA during this study. In the two weight groups the mean gestation and birth weight did not differ significantly between those that did and did not develop a HSDA (table 1).

Before the beginning of this study, the diagnosis of a HSDA in this unit was made from the development of clinical signs and then confirmed by echocardiography. In order that prospective echocardiography did not change clinical practice with regard to support of blood pressure, it was agreed with the doctors in charge of the infants that they would be blind to the echocardiographic findings unless there were specific clinical concerns, in which instance the findings would be made known to them. The current clinical practice on this unit with respect to blood pressure in very low birthweight infants is to try to maintain the mean blood pressure at or above 30 mm Hg. Initially plasma or blood are used as volume expanders, with 10 ml/kg given over 30 minutes and repeated if necessary. If the response is not maintained dopamine is started at a dose of 5 µg/kg/min and increased if necessary to a maximum of 20 µg/kg/min.

Table 1 *Gestation and birth weight of infants with and without a HSDA*

	Infants with HSDA (LA:Ao >1·5)	*Infants without HSDA (LA:Ao <1·5)*
Infants 1000–1500 g		
Mean (range) gestation (weeks)	28·8 (27–31)*	29·2 (27–31)†
Mean (range) birth weight (g)	1200 (1005–1500)*	1250 (1009–1500)†
Infants <1000 g		
Mean (range) gestation (weeks)	25·8 (24–29)‡	26·6 (24–30)‡
Mean (range) birth weight (g)	700 (500–950)‡	780 (620–940)‡

*n=12, †n=13, ‡n=8

The study was approved by the central Oxford regional ethics committee. Statistical analysis was by unpaired Student's t test, Wilcoxon rank sum test, and the χ^2 test. Significance was accepted at p values of less than 0·05.

Results

WEIGHT GROUP 1000–1500 g

Blood pressure

Over the first five days of life the average mean blood pressure was slightly lower in the group with a HSDA (fig 1). The differences were small and not statistically significant. Mean systolic blood pressure and mean diastolic blood pressure were lower by similar amounts in the group with a HSDA with no disproportionate reduction in diastolic blood pressure (fig 2). Again the differences were small and not significant. As a result of the mean pulse pressure did not differ between the two groups. Table 2 gives the number of studies for each group on each day.

Further subdividing the infants with a HSDA into weight groups 1000–1200 g and

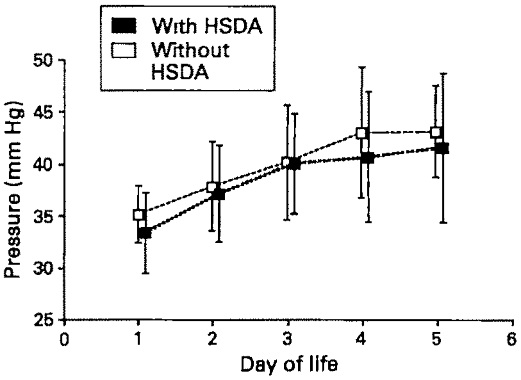

Figure 1 Mean (SD) mean blood pressure in infants 1000–1500 g comparing those with a HSDA with those without.

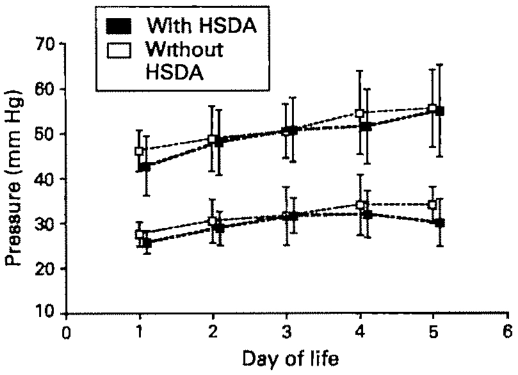

Figure 2 Mean (SD) systolic blood pressure (upper two lines) and mean diastolic blood pressure (lower two lines) in infants 1000–1500 g comparing those with a HSDA with those without

Table 2 Number of studies on each day after birth for each weight group

Day of life	*Infants 1000–1500 g*		*Infants <1000 g*	
	HSDA	*No HSDA*	*HSDA*	*No HSDA*
1	5	18	7	6
2	9	15	7	8
3	11	13	6	9
4	8	13	8	7
5	7	10	7	8
6	—	—	7	9
7	—	—	7	8

1201–1500 g did not change this analysis. The five day cumulative mean mean blood pressure values were 39 and 37·4 mm Hg respectively.

Respiratory disease

Criteria of acute respiratory disease severity are compared in table 3 for those with and without a HSDA in this weight group. Mean maximum fractional inspired oxygen ($F\text{IO}_2$) and time spent in $F\text{IO}_2$ >0·5 did not differ; however, the mean maximum mean airway pressure (MAP) was significantly higher in those infants with a HSDA.

Complications

The incidence of complications which might also be associated with low blood pressure are compared in table 4. None of the differences is significant.

WEIGHT GROUP <1000 g

Blood pressure

Over the first seven days the average mean blood pressure was significantly lower in the group with a HSDA (fig 3). The mean systolic blood pressure was not consistently significantly lower until day 4, the difference just reaching significance on day 1 (p=0·03) but not on days 2 and 3 (fig. 4). Mean diastolic blood pressure was significantly lower in those with a HSDA throughout the week, with all the infants' diastolic blood pressure falling into a narrow band between 20 and 24 mm Hg by day 7 (fig 4). Mean pulse pressure did not differ significantly between the two groups. The number of studies on each day for each group are shown in table 2.

Respiratory disease

Parameters of respiratory disease severity are compared for this group in table 3. There are no significant differences between those with and without a HSDA.

Table 3 Parameters of acute respiratory disease in infants studied

	Infants with HSDA (LA·Ao >1 5)	*Infants without HSDA (LA·Ao <1·5)*
Infants 1000–1500 g		
Mean (SD) maximum $F\text{IO}_2$	0 71 (0·25)*	0 6 (0·21)†
Mean (SD) maximum MAP (cm H_2O)	11·5 (3 5)*	7 9** (3·1)†
Mean (SD) time $F\text{IO}_2$ >0·05 (hours)	61·25 (38·9)*	59 (36)†
Infants <1000 g		
Mean (SD) maximum $F\text{IO}_2$	0 57 (0 3)‡	0·57 (0 3)‡
Mean (SD) maximum MAP (cm H_2O)	9·9 (2·8)‡	4 6 (4·6)‡
Mean (SD) time $F\text{IO}_2$ >0 05 (hours)	41 4 (54)‡	41 9 (46)‡

*n=12, †n=13; ‡n=8 **p<0 05.

Table 4 Complication rates in infants studied. Results given as No (%) of infants

	Infants with HSDA (LA·Ao >1 5)	*Infants without HSDA (LA·Ao <1 5)*
Infants 1000–1500 g		
IVH (grade 2 or more)	7 (58)*	3 (23)†
Pneumothorax	2 (16)*	4 (131)†
Infection	1 (7 5)*	0
Infants <1000 g		
IVH (grade 2 or more)	3 (37)‡	2 (25)‡
Pneumothorax	1 (12)‡	2 (25)‡
Infection	1 (12·5)‡	1 (12 5)‡

IVH, intraventricular haemorrahge. *n=12, †n=13, ‡n=8

Complications

The incidences of complications associated with low blood pressure are compared in table 4. None of the differences is significant.

Treatment for hypotension

Over the first five days the infants with a HSDA received a mean of 15·7 ml/kg of plasma compared with 8·2 ml/kg in those with no HSDA. Four of the eight in this group with a HSDA required a dopamine infusion to maintain an acceptable blood pressure compared with one of eight in those with no

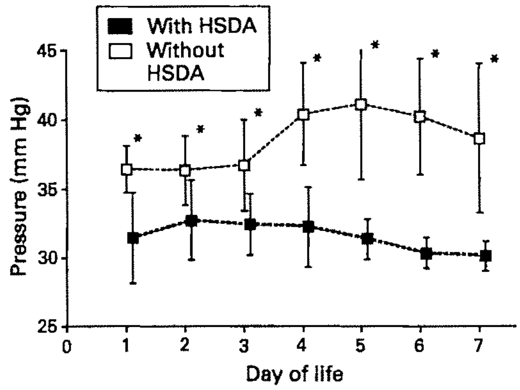

*Figure 3 Mean (SD) mean blood pressure in infants <1000 g comparing those with a HSDA with those without; *p<0·05*

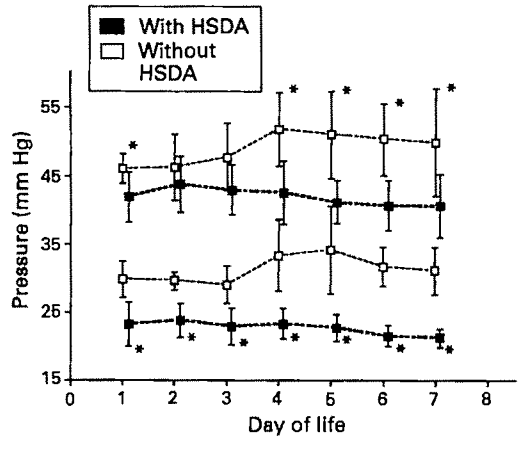

*Figure 4 Mean (SD) systolic blood pressure and mean diastolic blood pressure in infants <1000 g comparing those with a HSDA with those without; *p<0·05.*

HSDA. Neither of these differences reach statistical significance.

Discussion

This study has shown that a HSDA in very preterm infants over the first week of life is associated with a reduction in both systolic blood pressure and diastolic blood pressure and as a result the pulse pressure is not significantly affected. This is in keeping with the findings of Ratner *et al.*[3] In contrast to Ratner's study, however, we have shown the most dramatic reductions in blood pressure in those infants of <1000 g. Ratner did not look separately at this group of infants, analysing data on all infants of <1200 g. In our analysis the mean blood pressure in those with a HSDA did not differ significantly between infants of 1000–1200 g and those of 1201–1500 g.

In basic physiological terms blood pressure is a product of cardiac output and systemic vascular resistance. Although systolic blood pressure and diastolic blood pressure are affected by both these factors, systolic pressure is more affected by changes in cardiac output, particularly in stroke volume and ejection velocity, and diastolic pressure is more affected by changes in systemic vascular resistance.[5] In subjects with normal myocardial function and reserve, the left ventricle will respond to the increased volume load produced by a left to right ductal shunt by increasing stroke volume and consequently peak ejection velocity. As a result systolic pressure will be relatively protected whereas diastolic pressure will decrease due to the effect of the patent duct on systemic vascular resistance.

The immature myocardium of the very preterm infant has incomplete sympathetic innervation and less contractile tissue mass[6] and so will have less reserve to cope with the volume load which results from a large ductal shunt. There is, however, evidence from studies on preterm animals[7] and humans[8] that, particularly in the first few days of life, the immature heart is capable of producing fairly significant increases in cardiac output in response to ductal shunting. Baylen *et al* pointed out that in preterm lambs cardiac output was maintained at the expense of increasing left ventricular end diastolic volume and speculated that the immature myocardium might be unable to sustain this response over a period of time.[7] Rudolf *et al* described two patterns of haemodynamic response to large artificial aortopulmonary communication in dogs: one in which arterial pressure was maintained with increased cardiac output as already described and the other, seen in older dogs, where output and arterial pressure decreased.[9] They speculated that the latter response reflected less myocardial reserve. In our study the infants >1000 g with a HSDA had slightly but not significantly lower systolic pressures, suggesting that on the whole these infants can increase output to protect pressures in line with the first response described by Rudolf *et al.*[9] In contrast the infants <1000 g with a HSDA had markedly lower systolic pressures. Systolic pressure in this group was not consistently significantly lower until after day three, suggesting that some of these infants may have produced an initial compensatory increase in cardiac output which then failed in line with the second response described by Rudolf *et al.*[9]

The patent duct also causes a decrease in diastolic pressure by reducing systemic vascular resistance. In the infants >1000 g the diastolic pressure was not significantly lower in those with a HSDA. The effect the patent duct has on systemic vascular resistance will in turn be dependent on the pulmonary vascular resistance. Most of these infants had hyaline membrane disease and so pulmonary vascular resistance is likely to have been high.[2] This would reduce the effect of the duct on systemic vascular resistance. Despite this the usual direction of shunting was left to right and by the LA:Ao ratio criteria most became significant within three days of birth. This is in line with the observations of other workers[8 10] and is not inconsistent with the presence of increased pulmonary vascular resistance. The diameter of the defect, as well as the pressure differential, will be an important determinant of shunt size. We have observed anecdotally that the diameter of the ductus arteriosus is greatest in the first few days of life with a tendency to decrease in size with age.

In contrast the infants <1000 g with a HSDA had consistently and significantly lower diastolic pressures. This may have reflected the cumulative effect of myocardial failure and reduced systemic vascular resistance; on the whole this group had less severe acute respiratory problems.

In all infants with a HSDA the consequence of similiar reductions in systolic blood pressure and diastolic blood pressure is that the pulse pressure was not significantly affected. This implies that a widened pulse pressure is not a useful physical sign in the first week of life. Despite this many of the infants with a HSDA did develop full pulses. This suggests that other factors may also be important in the perception of full pulses, such as increased left ventricular stroke volume and ejection velocity. This study was made during the first week after birth; we limited it to this period firstly because this is the important period diagnostically and secondly because this is the time that blood pressure is most consistently monitored for clinical reasons. With increasing age it might be expected that the more classical picture would emerge, firstly because pulmonary vascular resistance will fall and secondly because hypertrophy will start to compensate for the lack of myocardial reserve.

The significant hypotension seen in several of the infants <1000 g with HSDA is reflected in the higher use of volume expanders and inotropes. If a HSDA is the cause of hypotension in these infants then neither of these treatments are appropriate. Plasma and blood products will increase the volume load on an already volume overloaded heart. In addition, although dopamine will have an inotropic effect, it will also increase systemic vascular resistance which could theoretically increase the left to right shunt. The most appropriate treatment would be medical or surgical closure of the ductus arteriosus.

This study has shown that the haemodynamic effects of HSDA can be demonstrated well before it becomes clinically apparent and that in extremely low birthweight infants the possibility of a clinically silent HSDA should be considered before large volumes of plasma expanders are given to treat hypotension.

We thank Drs Andrew Wilkinson, Peter Hope, and Kevin Ives for their help and advice and for allowing us to study the infants under their care

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Annual audit of neonatal morbidity in preterm infants

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Abstract

Annual odds ratios, standardised for known confounding variables, were used to examine trends in major neonatal morbidities among 3220 preterm infants of less than 35 weeks' gestation admitted to a regional referral centre between 1980 and 1991. Despite improved survival, the risk of major cerebral haemorrhage, ventriculoperitoneal shunt insertion, and necrotising enterocolitis was unchanged. A recent reduction in risk of pneumothorax and persistence of the arterial duct was noted. An increased risk for chronic lung disease over time could be accounted for by increased survival, although a similar increase in risk for infection remained unexplained.

(*Arch Dis Child* 1992; 67: 1174–6)

Medical audit aims to examine critically the structure, process, and outcome of medical care. In the field of neonatal intensive care, while structure and process are relatively easy to assess, it is often difficult to interpret the significance of observed differences in outcome between centres or over time. Data concerning the outcome of neonatal intensive care, by the nature of the specialty, are largely derived from referral centres, whose patient populations are subject to selection biases. Outcome in terms of survival and neonatal morbidity are well known to be affected by variables such as birth weight, gestation, sex, multiple pregnancy, mode of delivery, and place of birth. Differences in outcome between centres or from year to year in a single centre may be due to changes in population variables such as these, rather than to any response to medical intervention or management. Similarly, where morbidity is contingent upon neonatal survival, changes in survival alone may alter the prevalence of morbidity. In order to be able to interpret changes in neonatal morbidity in preterm infants over time in a single referral centre, annual trends have been examined after standardisation for known confounding variables and the effect of improved survival.

Table 1 Definitions of descriptive and outcome variables used in the analyses

Descriptive variables:	
Birth weight	Birth weight in grams
Gestation	Gestational age in completed weeks
Sex	Male/female
Multiple pregnancy	Yes/no
Mode of delivery	Vaginal/caesarean section
Place of birth	Inborn/outborn
Outcome variables:	
Survival	Survival to discharge from unit
Parenchymal haemorrhage	Ultrasound scan evidence of parenchymal haemorrhage or infarction
BPD	Oxygen dependency at 28 days with radiographic changes in previously ventilated infant
Ventriculoperitoneal shunt	Treatment of hydrocephaly by insertion of ventriculoperitoneal or atrial shunt
Pneumothorax	Pneumothorax treated by thoracocentesis
Persistent ductus arteriosus	Clinical diagnosis of ductal shunt which resulted in change in management
Septicaemia	Positive blood culture
Necrotising enterocolitis	Clinical diagnosis supported by radiographic, surgical, or necropsy findings

Table 2 Descriptive variables that significantly changed over the study period

	1980	*1981*	*1982*	*1983*	*1984*	*1985*	*1986*	*1987*	*1988*	*1989*	*1990*	*1991*
Outborn	78	86	94	85	76	81	77	88	58	73	65	62
Inborn	147	183	195	234	205	204	207	183	161	189	208	181
(%)	(65)	(68)	(67)	(73)	(73)	(71)	(73)	(67)	(73)	(72)	(76)	(74)
	χ^2 for trend, 7·55, p=0·006											
Vaginal delivery	155	164	178	191	140	149	128	154	123	125	145	145
Caesarean section	70	105	111	127	141	136	156	117	96	137	128	98
(%)	(31)	(39)	(38)	(40)	(50)	(48)	(55)	(43)	(44)	(52)	(47)	(40)
	χ^2 for trend, 13·9, p=0·0002											
Gestation (weeks)												
<28	44	59	52	58	46	54	58	60	54	57	55	59
28–31	87	108	128	126	120	127	144	117	81	106	101	97
32–34	94	102	109	135	115	107	82	94	84	99	117	87
	χ^2 for trend, 6·1, p=0·01											

Patients and methods

All infants of less than 35 weeks' gestation admitted to the Mersey Regional Intensive and Special Care Unit between 1 January 1980 and 31 December 1991 were included in the study. By using the admission registers, case records, cranial ultrasound records, and microfilmed intensive care sheets the year of birth and descriptive and outcome variables were obtained for each infant (table 1). The descriptive variables were cross tabulated with the year of birth to examine for changes in the nature of the patient population over the 12 year period. The same variables were then similarly compared with the outcome variables to see which might act as confounding variables when trends in annual prevalence of the outcomes was examined. Each outcome variable was then entered into a logistic regression analysis as the dependent variable with each year and the identified confounding variables as the independent variables. From the analyses, the odds ratio and its 95% confidence interval for the risk of each outcome for every year compared with 1980, and standardised for the other significantly related variables, was obtained. For outcomes where the odds ratio significantly changed over the period studied, a further analysis was performed including death and/or that outcome

Table 3 Outcome variables whose incidence was related to the descriptive variables on cross tabulation

	Survival	*Parenchymal haemorrhage*	*Ventriculo-peritoneal shunt*	*BPD*	*Pneumothorax*	*Persistent ductus arteriosus*	*Septicaemia*	*Necrotising enterocolitis*
Multiple	0·74	0·10	0·26	0·04	0·47	0·79	0·12	0·97
Inborn	<0·001	<0·001	<0·001	<0·001	<0·001	<0·001	<0·001	<0·001
Sex	0·01	0·93	0·04	0·31	0·14	0·03	0·63	0·39
Caesarean section	<0·001	0·001	0·75	0·37	0·40	0·43	0·83	0·96
Gestation	<0·001	<0·001	<0·001	<0·001	<0·001	<0·001	<0·001	<0·001
Birth weight	<0·001	<0·001	<0·001	<0·001	<0·001	<0·001	<0·001	<0·001

Exact probabilities are used except where shown

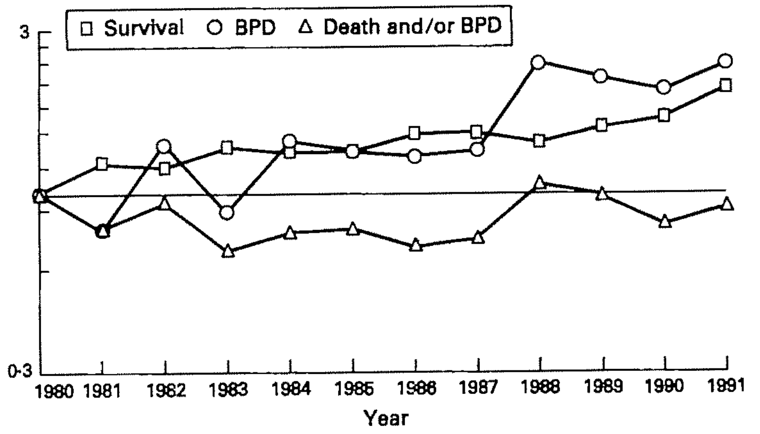

Figure 1 Annual odds ratios for survival, BPD, and death and/or BPD, 95% confidence intervals are omitted for clarity.

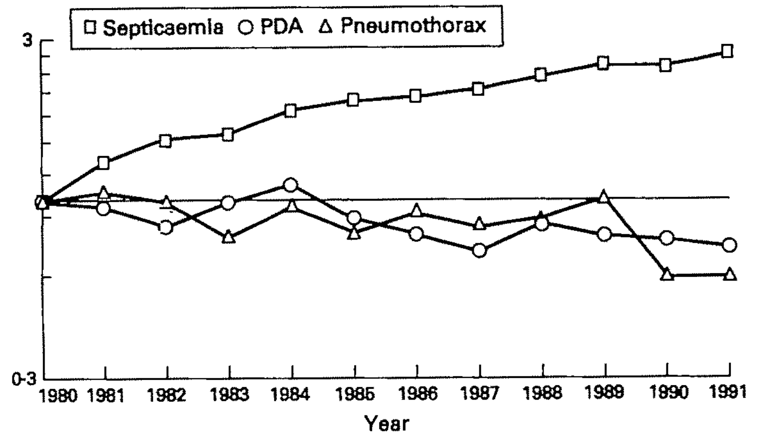

Figure 2 Annual odds ratios for septicaemia, persistent ductus arteriosus (PDA), and pneumothorax, 95% confidence intervals have been omitted for clarity

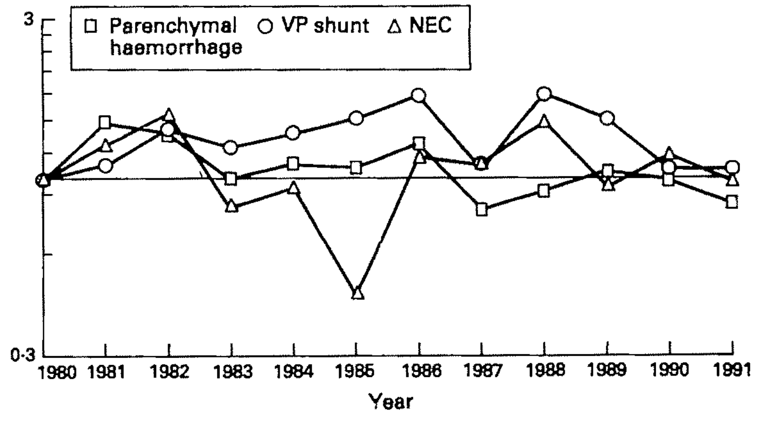

Figure 3 Annual odds ratios for parenchymal haemorrhage, ventriculoperitoneal (VP) shunt, and necrotising enterocolitis (NEC); 95% confidence intervals have been omitted for clarity.

as an independent variable to correct for the effect of improved survival, and the resulting odds ratios re-examined.

The χ^2 test and χ^2 test for trend were used to test for significance in the cross tabulations, and the logistic regression was performed using the Logit option of the Probit program in SPSS-X Release 3·1[1]

Results

A total of 3220 infants were included in the study. Data were complete apart from cranial ultrasound scans that were not performed on 431 infants who were either larger well infants or those with lethal malformations. Of the descriptive variables, lower gestation, and increased frequency of caesarean section and inborn delivery were seen in more recent years (table 2). Outcomes were significantly associated with gestation, birth weight, inborn delivery, sex, and birth by caesarean section (table 3). The odds ratios for survival, bronchopulmonary dysplasia (BPD) and septicaemia increased for more recent years (figs 1, 2, and tables 4, 5). A trend to reduction of risk for pneumothorax and persistent ductus arteriosus was seen (fig 2, table 5), but not for parenchymal cerebral haemorrhage, insertion of a ventriculoperitoneal shunt, or necrotising enterocolitis (fig 3).

The effect of increased survival in more recent years was taken into account by calculating the odds ratios for 'death and/or BPD' for each year. In no year did these significantly exceed 1 (fig 1, table 4). A similar calculation for septicaemia showed a residual trend to increased risk in recent years.

Discussion

Using a logistic regression technique, it has been possible to examine trends in survival and neonatal morbidity over a 12 year period after standardising for known confounding variables. Despite the marked improvement in survival in recent years, morbidities such as major cerebral haemorrhage and infarction, shunted hydrocephalus, and necrotising enterocolitis are as likely to occur now as in 1980. The occurrence of persistent ductus arteriosus and pneumothorax have also remained substantially unchanged except in the last year or two when both have been significantly less likely to occur. The greatest improvements in the chance of survival have also been in the last two years. A possible explanation for these findings is the introduction of surfactant treatment for all infants likely to benefit from it. Reduction of persistent ductus arteriosus and pneumothorax as well as improved survival have been noted as important effects of surfactant treatment.[2] There has been a significant increase in the risk of BPD. While it has been possible to show that specific factors may be responsible for this increase in high risk subgroups,[3] the overall trend to higher risk for developing BPD may simply be related to increased survival of very preterm infants. When the risk of death and/or BPD is examined, the odds ratio for this outcome does not significantly exceed 1 in any year, suggesting that most of the increased occurrence of BPD is indeed related to improved survival. The risk of septicaemia has continued to increase over the study period, and could also be related to improved survival of high risk infants. After standardising for survival in a similar way, however, the increasing risk for septicaemia over the years persisted. It may be that a variable such as increased duration of stay in the unit is more important.

Table 4 Annual odds ratios (with 95% confidence intervals) for survival, BPD, and death and/or BPD

Year	*Survival*	*BPD*	*Death and/or BPD*
1981	1·22 (0·96 to 1·55)	0·73 (0·48 to 1·27)	0·78 (0·60 to 0·98)
1982	1·19 (0·94 to 1·52)	1·39 (0·92 to 2·10)	0·94 (0·73 to 1·19)
1983	1·36 (1·08 to 1·75)	0·83 (0·56 to 1·41)	0·68 (0·53 to 0·87)
1984	1·31 (1·02 to 1·68)	1·4[illegible] (0·94 to 2·13)	0·77 (0·60 to 1·98)
1985	1·32 (1·04 to 1·70)	1·32 (0·87 to 2·00)	0·79 (0·62 to 0·01)
1986	1·48 (1·15 to 1·89)	1·2[illegible] (0·84 to 1·94)	0·70 (0·55 to 1·90)
1987	1·50 (1·18 to 1·94)	1·33 (0·89 to 2·01)	0·74 (0·58 to 1·95)
1988	1·40 (1·09 to 1·84)	2·36 (1·61 to 3·49)	1·06 (0·82 to 1·36)
1989	1·55 (1·20 to 2·01)	2·16 (1·47 to 3·18)	0·98 (0·77 to 1·26)
1990	1·65 (1·27 to 2·15)	1·99 (1·35 to 2·94)	0·81 (0·63 to 1·04)
1991	2·08 (1·57 to 2·76)	2·37 (1·61 to 3·48)	0·91 (0·71 to 1·18)

Table 5 Annual odds ratios (with 95% confidence intervals) for septicaemia, persistent ductus arteriosus, and pneumothorax

Year	*Septicaemia*	*Persistent ductus arteriosus*	*Pneumothorax*
1981	1·30 (0·97 to 1·74)	0·96 (0·75 to 1·22)	1·06 (0·82 to 1·37)
1982	1·52 (1·15 to 2·01)	0·84 (0·65 to 1·07)	0·99 (0·82 to 1·37)
1983	1·57 (1·19 to 2·07)	0·99 (0·78 to 1·25)	0·78 (0·60 to 1·03)
1984	1·84 (1·39 to 2·12)	1·11 (0·88 to 1·40)	0·96 (0·74 to 1·25)
1985	1·96 (1·49 to 2·58)	0·88 (0·59 to 1·13)	0·80 (0·61 to 1·06)
1986	2·01 (1·53 to 2·64)	0·79 (0·62 to 1·03)	0·92 (0·71 to 1·19)
1987	2·11 (1·61 to 2·78)	0·70 (0·52 to 0·89)	0·83 (0·63 to 1·08)
1988	2·29 (1·73 to 3·03)	0·85 (0·64 to 1·11)	0·88 (0·67 to 1·17)
1989	2·48 (1·98 to 3·25)	0·78 (0·60 to 1·01)	1·01 (0·78 to 1·31)
1990	2·45 (2·00 to 3·57)	0·76 (0·58 to 0·99)	0·85 (0·64 to 1·11)
1991	2·66 (2·00 to 3·57)	0·72 (0·54 to 0·94)	0·59 (0·42 to 0·82)

The use of an audit method as described can be an ongoing process, and may identify real changes in morbidity over time in a large referral centre, allowing assessment of the effect of management policies, and the highlighting of problems requiring further study.

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Prediction of neurodevelopmental outcome in the preterm infant: short latency cortical somatosensory evoked potentials compared with cranial ultrasound

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Abstract

One hundred and twenty six preterm infants, with a gestational age of 34 weeks or less, were studied to compare the predictive value of somatosensory evoked potentials (SEPs) with that of cranial ultrasound. A normal N1 latency was no guarantee of a normal outcome, nor did a persistently delayed N1 latency always correlate with a poor outcome. As a predictor of cerebral palsy, SEPs had a sensitivity of 44% and a specificity of 92%. The presence of a large haemorrhage (grade IIb/III) or cystic leucomalacia on cranial ultrasound predicted cerebral palsy with a sensitivity of 73·6% and a specificity of 83·1%. These results demonstrate that the role of SEPs recorded after median nerve stimulation is limited in preterm infants.

(*Arch Dis Child* 1992;67:1177–81)

With an ever increasing number of surviving low birthweight infants and an increase in the total number of premature infants who develop cerebral palsy, attempts have been made to improve early prediction of neurodevelopmental outcome in these at risk infants.[1] Cranial ultrasound has played an important part and the presence of extensive cystic periventricular leucomalacia is now acknowledged by many groups to correlate strongly with the development of cerebral palsy.[2 3] It is more complicated to predict the neurodevelopment of infants with other ultrasound abnormalities, like large intraventricular haemorrhages and transient densities, as a large number of these infants survive to be normal in spite of the lesion.[2 4 5] Other modes of investigation, such as magnetic resonance spectroscopy,[6] electroencephalography,[7] and somatosensory evoked potentials (SEPs)[8–10] have been used trying to identify those infants who are to survive with a major handicap. Previous studies using SEPs showed a good correlation between this test and subsequent neurodevelopment, but the number of infants tested in each study tended to be small.[8–10]

The aim of this study was to study prospectively a population of preterm infants in order to evaluate further the role of SEPs in the prediction of neurodevelopmental outcome and to compare the predictive value of SEPs and cranial ultrasound.

Patients and methods

Over 26 months, 126 premature infants were entered into a prospective correlative study of short latency SEPs and cranial ultrasonography. All infants had a gestational age of 34 weeks or less with a mean gestational age at birth of 30·2 weeks (range 25–34 weeks). Twenty one of the 126 infants were small for gestational age. Informed parental consent was obtained in all infants before entering the study.

ULTRASOUND ASSESSMENT

Ultrasound assessment was performed at least twice a week during the first week of life and twice a week thereafter until discharge, using an ATL UM-4 mechanical sector scanner (5–7·5–10 MHz crystal). Periventricular–intraventricular haemorrhage (PVH–IVH) and periventricular leucomalacia (PVL) were graded as reported previously.[11 12]

PVH–IVH

Grade I: small germinal layer haemorrhage; grade IIa: germinal layer haemorrhage plus IVH, filling the ventricle <50%; grade IIb: large IVH distending the ventricle in the acute phase, due to blood filling the ventricle >50%; grade III: unilateral parenchymal involvement, due to venous or haemorrhagic infarction.

Leucomalacia

Transient densities: periventricular areas of increased echogenicity, present for seven days or more. Cystic PVL: periventricular areas of increased echogenicity evolving into extensive cystic lesions, involving the occipital with or without the frontoparietal periventricular white matter.

For correlation of cranial ultrasound lesions with subsequent neurodevelopmental outcome the maximum degree of haemorrhage, in case of extension, and the eventual evolution of echogenic areas into cystic lesions or not, were taken into account.

SEPS
Somatosensory evoked potentials were recorded with a Nihon Kohden Neuropack II or IV. Silver/silver chloride disc electrodes were applied: the negative electrode on C3' or C4', the positive on Fz and the neutral one on the lower arm. The impedance was less than 2 kOhms. Electrical stimuli of 0·1 msec duration were delivered at a rate of 1/two seconds. A hand held device was used, which was placed on the ventral wrist overlying the median nerve. The stimulation intensity used was that necessary to produce a minimal thumb twitch. Recordings were obtained from the left somatosensory cortex after stimulation of the right median nerve. Recordings were obtained from both hemispheres when a unilateral lesion was present on cranial ultrasound examination. A total of 50–128 responses was averaged through a bandpass of 2–100 Hz. Each trial was repeated two to three times to ensure reproducibility. The analysis time was 200 msec. The latency to the peak of the first negative wave (N1) was measured according to the criteria of Desmedt *et al*.[13] All infants were tested without sedation after a feed. The filter settings, stimulation rate, and duration were the same as those of Klimach and Cooke so their normal data were used.[14]

All infants were tested for the first time in a stable condition, usually beyond the end of the first week.[15] Sequential studies were performed in 69 of the 126 infants. In infants with a normal N1 latency on the first examination sequential studies were performed in those who were taking part in a longitudinal study[15] and in infants who had any clinical deterioration or developed abnormalities on cranial ultrasound. In infants with an N1 latency outside the normal range, that is delayed, or when it was not possible to obtain a response, SEPs were repeated at 40 weeks' postmenstrual age. When the N1 latency had normalised at 40 weeks' postmenstrual age, this last N1 latency was used for correlation with neurodevelopmental outcome.

NEUROLOGICAL ASSESSMENT OF OUTCOME
Assessment of outcome was made on clinical examination at discharge from the neonatal unit using the standardised Dubowitz protocol[16] and at 6, 12, and 18 months corrected for prematurity using Griffiths's mental development scale and items from the scores of Amiel-Tison and Grenier[17] and Touwen.[18] All of the children were last seen when at least 12 months of age corrected for prematurity. Five of the 126 infants were not seen at our follow up clinic and follow up information was obtained from the paediatrician at the referring district general hospital. The children were grouped in three categories. (A) Normal; when the developmental quotient was more than 90 and no neurological, visual, or hearing abnormalities were present. (B) Some abnormality of tone pattern ('dystonia') on at least two separate occasions, but functionally normal.[19] (C) Definite neurological handicap, cerebral palsy and/or severe hearing or visual defects.

For the purpose of calculating properties such as sensitivity and specificity infants in group B were analysed with those in group A as it is well recognised that infants with transient dystonia only have transient abnormalities in tone.[19]

Results

SEPS
A total number of 240 recordings were done, with a mean of 1·9 recordings per infant (range 1–11). In 107 of the 126 infants a normal N1 latency was obtained. Fifty eight of these 107 infants had their first examination before the end of the third week, 48 having a normal N1 latency on their first examination and 10 normalising before reaching 40 weeks' postmenstrual age. In 19 infants the N1 latency was delayed, being still outside the 95% tolerance limit at 40 weeks' postmenstrual age.

Table 1 Neurodevelopmental outcome at ≥12 months and N1 latency at 40 weeks' postmenstrual age

Outcome	*Normal*	*Transient dystonia*	*Cerebral palsy*	*Total*
Normal N1 latency	82 (1*)	11	14	107
Delayed N1 latency	2	6	11 (1*)	19

*=Blind due to retinopathy of prematurity

Table 2 Neurodevelopmental outcome at ≥12 months of age and occurrence and grade of PVH–IVH and leucomalacia

Outcome	*Normal*	*Transient dystonia*	*Cerebral palsy*	*Total*
Normal scan	43	6	0	49
PVH–IVH				
Grade I–IIa	15	4	1	20
Grade IIb	7	2	1	10
Grade III	8(1*)	0	7 (1*)	15
Leucomalacia				
Transient densities	11	5	4	20
Cystic PVL	0	0	12	12
				126

*=Blind due to retinopathy of prematurity

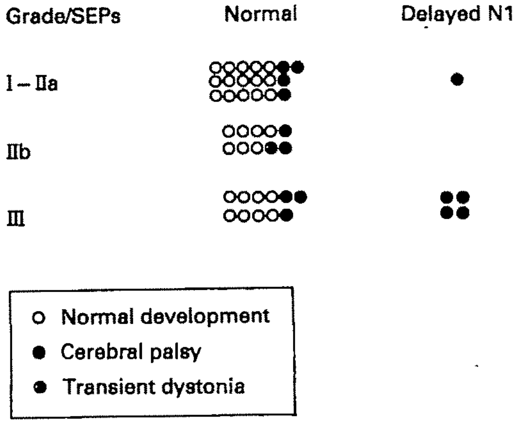

Figure 1 Correlation of SEPs at 40 weeks' postmenstrual age, ultrasound abnormalities (PVH–IVH) and neurological outcome in 45 infants.

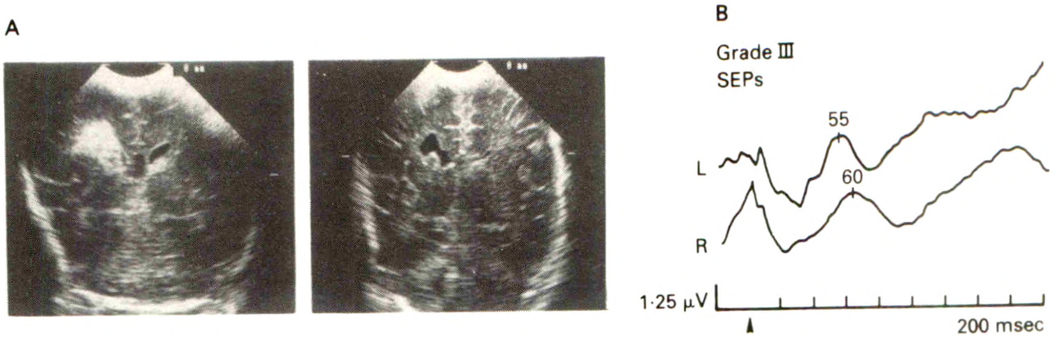

Figure 2 (A) Cranial ultrasound, coronal view, showing a grade III haemorrhage on the right, evolving into a porencephalic cyst. (B) SEPs recorded from the same infant at 36 weeks' postmenstrual age, showing a slight difference in N1 latency, being within the 95% tolerance limit of Klimach and Cooke in both hemispheres.

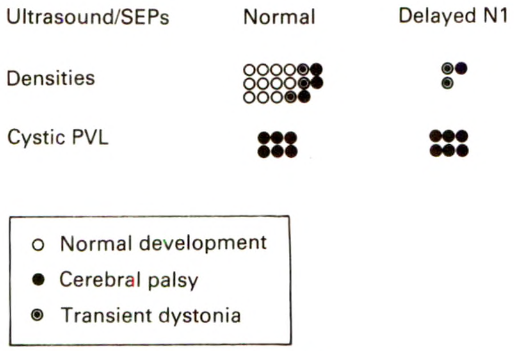

Figure 3 Correlation of SEPs at 40 weeks' postmenstrual age, ultrasound abnormalities (leucomalacia) and neurological outcome in 32 infants.

CORRELATION OF SEPS WITH NEUROLOGICAL OUTCOME

A normal N1 latency was not invariably associated with a normal outcome (table 1). Fourteen infants with a normal N1 latency at 40 weeks' postmenstrual age developed cerebral palsy. Longitudinal studies (2–8 times) were performed in 10 of these infants, and six of them initially had a delayed N1 latency.

If the sequential recordings for SEPs were persistently abnormal, the outcome was almost never completely normal. Of the 19 infants with a persistently delayed N1 latency, 11 developed cerebral palsy, six developed transient dystonia, and only two were normal at follow up. Seven of the eight infants with a delayed N1 latency, and who did not develop cerebral palsy, were small for gestational age. As a predictor of cerebral palsy the SEPs had a sensitivity of 44% and a specificity of 92%. The predictive value of a positive test was 57·8% and that of a negative test was 87%.

CORRELATION OF CRANIAL ULTRASOUND WITH NEUROLOGICAL OUTCOME

In this cohort a normal ultrasound scan was never associated with the development of cerebral palsy and only six of the 49 infants with a normal scan developed transient dystonia (table 2). Of the 25 infants with large intraventricular haemorrhage with (III) or without (IIb) parenchymal involvement, 15 were found to be normal at early follow up and eight developed cerebral palsy. Of the 20 infants with transient densities, only 11 were normal at follow up, six developed transient dystonia, and four developed cerebral palsy. Cystic PVL was invariably associated with a poor outcome and all 12 infants developed cerebral palsy.

As a predictor for cerebral palsy severe ultrasound abnormalities (grade IIb–III haemorrhage and cystic PVL) had a sensitivity of 73·6%, a specificity of 83·1%, a positive predictive value of 45·1%, and a negative predictive value of 94·3%.

CORRELATION OF SEPS AND ULTRASOUND FINDINGS WITH NEURODEVELOPMENTAL OUTCOME.

All 35 infants who were of appropriate weight for gestational age without ultrasound abnormalities had a normal N1 latency and only one of them developed transient dystonia. Of the 14 infants who were small for gestational age without ultrasound abnormalities, five infants

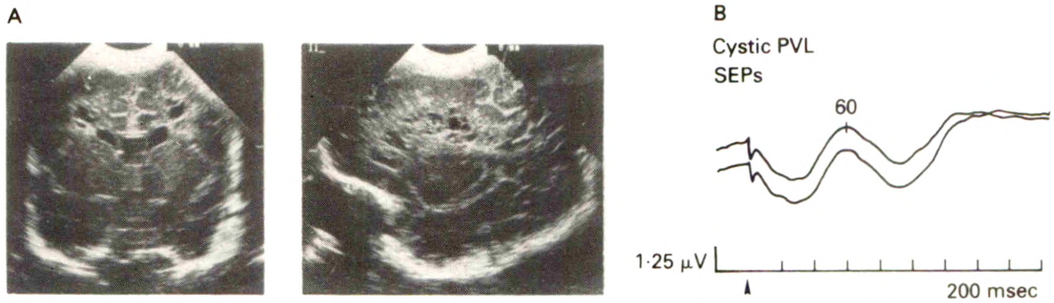

Figure 4 (A) Cranial ultrasound scan, showing extensive cystic PVL in the coronal (left) and parasagittal (right) view. (B) SEPs recorded from the same infant at 35 weeks' postmenstrual age, showing an N1 latency at 60 msec, which is within the 95% tolerance limit of Klimach and Cooke.

had a persistently delayed N1 latency and three of them showed transient dystonia at follow up.

Of the 45 infants with PVH-IVH (fig 1), 40 had a normal N1 latency. Transient dystonia occurred in five of them and five developed cerebral palsy. Of the five infants with persistently delayed N1 latency one showed transient dystonia and four developed cerebral palsy. It was of interest that 11 of the 15 infants with unilateral parenchymal involvement had a normal N1 latency recorded from both hemispheres (fig 2). Three of them developed cerebral palsy, one a hemiplegia and the other two, with a porencephalic cyst in the occipital white matter, suffered from hypotonic cerebral palsy and visual impairment. Four of the 15 infants had a persistently delayed N1 latency, being delayed on both sides in all four. All four developed a hemiplegia with upper motor neuron signs present on both sides.

Seventeen of the 20 infants with transient densities had a normal N1 latency (fig 3). Transient dystonia occurred in three and three developed cerebral palsy. Of the three infants with a delayed N1 latency, two developed transient dystonia and one cerebral palsy. Of the 12 infants with cystic PVL, six had a normal N1 latency, but all infants developed cerebral palsy (fig 4).

Only seven of the 77 infants with ultrasound abnormalities were small for gestational age. Three of them had a normal N1 latency with subsequently a normal outcome. Four infants had a persistently delayed N1 latency associated with a grade III haemorrhage in one, who developed cerebral palsy, and associated with transient densities in the other three, one of whom developed cerebral palsy and the other two developed transient dystonia.

When the presence of major ultrasound abnormalities (grade IIb–III, cystic PVL) and a delayed N1 latency were taken together as a predictor for cerebral palsy, the sensitivity was 40%, specificity 100%, positive predictive value 100%, and negative predictive value 78·4%.

Discussion

Previous studies, using SEPs in premature infants, for prediction of subsequent neurodevelopmental outcome have been quite promising.[8–10] The predictive value in the present study, looking at a large cohort of infants with and without abnormalities on cranial ultrasound, was not as good as expected. A normal N1 latency was no guarantee of a normal outcome. Fourteen of the 25 infants who developed cerebral palsy, both related to large haemorrhages as well as to cystic PVL, had a normal N1 latency at or even before 40 weeks' postmenstrual age. Although in some of these infants parenchymal involvement was in the occipital periventricular white matter, possibly not affecting the somatosensory tracts, this was not true for all cases. In some infants with extensive cystic leucomalacia, cysts were noted in the frontoparietal and occipital periventricular white matter. A persistently delayed N1 latency also did not always correlate with a poor outcome. Eleven of the 19 infants with a persistently delayed N1 latency developed cerebral palsy. Seven of the eight infants with a delayed N1 latency, who did not develop cerebral palsy, were small for gestational age and five of these seven infants did not have any abnormalities on cranial ultrasound.

Due to the high turnover in our tertiary intensive care unit it was not possible to study all infants at the same postmenstrual age. However, all infants with a delayed N1 latency on the initial recording had repeat studies until normalisation occurred or the infant had reached 40 weeks' postmenstrual age. Of the 14 infants who developed cerebral palsy in spite of a normal N1 latency at 40 weeks' postmenstrual age, 10 had longitudinal studies showing a change from a delayed N1 latency to a normal N1 latency in six infants and a repeatedly normal N1 latency in the other four infants. A delayed N1 latency after an initially normal N1 latency was noted only twice among the 69 infants studied sequentially. This was in both cases associated with posthaemorrhagic ventricular dilatation, being reversible in one, after shunt insertion.[20]

Only 35 infants admitted during the study period were of appropriate weight for gestational age and had no abnormalities on cranial ultrasound. Calculating the regression equation of the N1 latency for these 35 infants showed this equation to be almost equal to that of Klimach and Cooke.[14] As the same filter settings and stimulation rate were used, and their normal data were collected from 102 infants, it was decided to use their normal data.

The findings in the present cohort differ from previous reports in the literature. Klimach and Cooke studied 30 low birthweight infants with abnormalities on cranial ultrasound.[8] All infants with a normal N1 latency were normal at follow up and six infants with a persistently delayed N1 latency had an abnormal outcome. Majnemer *et al* presented preliminary findings of 44 low birthweight infants.[9] Infants with absent or persistently delayed responses were found to have a major handicap at follow up. The SEPs had a sensitivity of 79% and a specificity of 88%. Laget *et al* studied 43 infants with a hemiplegia, between 1 month and 13 years of age, and found absent responses in 12 and a decrease in amplitude in the other 31 infants from the contralateral hemisphere.[21] Of the six infants described in this present study who developed a hemiplegia, five had a delayed N1 latency and this was present in both hemispheres in four of them. This is in agreement with clinical findings as most of the infants who developed a hemiplegia after a grade III haemorrhage also tend to have upper motor neuron signs on the other side of the body. Using positron emission tomography in infants with this type of lesion Volpe *et al* showed that preterm infants with a grade III haemorrhage had changes in cerebral blood flow in the non-affected hemisphere as well.[22] Willis *et al* studied 39 infants with PVH–IVH at 2, 4, and 6 months' corrected age.[10] Their findings are more similar to ours as they found that 36% of the infants with normal SEPs at 2 months' corrected age did go on to develop moderate or severe abnormalities. Only 14% of the infants with normal SEPs on three occasions had a poor outcome. As the aim of our study was to assess whether it was possible to improve early prediction, the infants were studied only until the age of 40 weeks' postmenstrual age.

In none of these previous studies was a distinction made between infants who were of appropriate weight or small for gestational age. Gallai *et al*, however, also drew attention to a delay (of 5 msec) in N1 latency in small for gestational age infants.[23] Our findings suggest that especially when there is an increase in N1 latency it should be taken into account whether the infant is small for gestational age or not.

When a comparison was made between SEPs and cranial ultrasound, the latter technique was noted to be more sensitive. All infants with an ultrasound diagnosis of cystic PVL went on to develop cerebral palsy, but only six of the 12 infants had a delayed N1 latency. When the presence of major ultrasound abnormalities (grade IIb–III, cystic PVL) and a delayed N1 latency were taken together as a predictor for cerebral palsy, the sensitivity was not better, but specificity and positive predictive value both became a 100%. In an earlier study, using SEPs in full term infants with postasphyxial encephalopathy, SEPs of the median nerve appeared to be of value when trying to predict subsequent neurodevelopmental outcome,[24] and this was recently confirmed by other groups.[25 26] It is possible that SEPs after stimulation of the median nerve are less useful in the preterm infant as the legs are usually more severely affected than the arms. At present a study is being undertaken in our unit to compare SEPs of the posterior tibial nerve and the median nerve to find out whether the SEPs of the posterior tibial nerve will be of better predictive value.

SEPs of the median nerve appear to be of limited value as an early predictor of subsequent neurodevelopmental outcome in the preterm infant and should probably not be performed routinely in all low birthweight infants.

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Membrane humidification—a new method for humidification of respiratory gases in ventilator treatment of neonates

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Abstract

A humidifier system for neonatology that functions according to the 'membrane humidification' principle was subjected to a performance test in our laboratory. Humidification and heating of the respiratory gases took place in a module consisting of a net of hollow fibres placed inside the incubator. In 18 measurement combinations flow, respiratory gas temperature, and incubator temperature were varied. At respiratory gas temperatures within the range of 33–37°C the minimum international standard for the absolute air humidity in the respiratory gas was achieved or exceeded in all measurements. No controlled clinical tests regarding the importance and long term effects of different temperatures and different humidity levels in the inspiratory air are yet available for the ventilation treatment of neonates.

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Humidification of respiratory gases in ventilator treatment of neonates constitutes a problem that has not yet been solved optimally. Studies by Tarnow-Mordi *et al*[1] have shown that in day to day practice minimum standards for humidification of breathing gases[2] during ventilation of neonates are not fulfilled in the majority of the patients.

We have performed laboratory tests on a newly developed humidification system (Aquamod, Dräger), a so called 'membrane humidifier' that could better fulfil the requirements of application in neonates.

Functional principle of the device

The humidifier module basically consists of a multiple layer of membranes with fine pores of 10 Å size. Here the respiratory gases come into contact with heated water which is continuously pumped through the system. During this process, water molecules diffuse through the membrane leading to a 100% saturation. The module should be installed inside the incubator in order to keep a possible temperature drop along the tubing path to the patient as low as possible and so avoid formation of condensation. In addition, the membrane serves as a bacterial filter. The inspiratory gas temperature is measured near to the patient (20 cm from the Y piece), by means of a sensor, and is adjusted to the set temperature by servocontrol. There is an automatic cut-out mechanism to reduce the risk of exposure to dangerously high inspiratory gas temperature and an alarm in case of low inspired gas temperature and inadequate function of the pump.

Methods of measurement

The respiratory gas temperature was measured by means of thermoelements (NiCr-Ni: Impac Tastotherm D 700). We recorded the deviations between set temperature and inspiratory gas temperature near the endotracheal tube (6 cm from the Y piece). In addition, the air temperature drop inside the inspiratory tubing system was measured at two different points (20 and 6 cm from the Y piece). The relative air humidity near the endotracheal tube was measured in the inspiratory circuit at a distance of 3 cm from the Y piece by means of a capacitive measurement technique (Rotronic Hygroskop DT). The thermoelements and the capacitive sensors are not supplied with the commercial humidification system. The absolute air humidity was calculated from the respiratory gas temperatures and the relative humidity. The measurements were carried out at different ambient temperatures inside the incubator (33, 35, 37°C). The set flow of the ventilator was modified: 2, 6, and 16 l/minute. The setpoint temperature of the humidifier was 34 and 37°C. After modification of these parameters and a period of 15 minutes for stabilisation the measurements were carried on for a time of 60 minutes for each combination of temperatures and gas flow. The average of two measurements of inspiratory gas temperatures and relative humidity during this plateau phase were calculated. The ventilator circuit was connected to an artificial lung (volume 50 ml) inside the incubator. The measurements were performed in a single wall incubator at a room temperature of about 26°C. Ventilator parameters (Dräger Babylog 1) were: frequency 45/minute, inspiratory: expiratory ratio 1:2, peak pressure 20 mm Hg, positive and expiratory pressure 4 mm Hg. The results were recorded simultaneously on a recording instrument (BBC Goerz Metrawatt SE 460).

Results

RELATIVE AIR HUMIDITY

The measurements of the relative air humidity at the inspiratory tubing system near the endotracheal tube resulted in values in the range of 87·5 and 100% relative humidity (table).

Inspiratory gas temperature, relative humidity, and absolute humidity of inspired air with different combinations of flow, incubator temperature, and set temperature of the membrane humidifier system

Flow (l/min)	*Incubator temperature (°C)*	*Set temperature of Aquamod (°C)*	*Temperature at Y piece (°C)*	*Relative humidity (%)*	*Absolute humidity (mg water/l air)*
2	33	34	34·5	100	38
6	33·5	34	33·5	100	36
16	33·8	34	34	100	38
2	34	37	35	100	40
6	34	37	37	99	43·5
16	34	37	36	98	41
2	35	34	34	100	37
6	35	34	33	88	32
16	35	34	33	93·5	33
2	35·5	37	35·5	100	41
6	35·5	37	35·5	99·5	41
16	35·5	37	33·5	99·5	41
2	37	34	35	87·5	34·5
6	37	34	35	88	35
16	37	34	33·5	89	32·5
2	37	37	36·5	91·5	38
6	37	37	36	99	42
16	37	37	36	98	41

At the lower system temperature of 34°C relatively high air humidity values above 95% were only reached at incubator temperatures between 33 and 35°C. At an incubator temperature of 37°C the relative humidity was below 90°C regardless of flow.

At higher respiratory gas values of 37°C the relative humidity was below 95% only at an incubator temperature of 37°C and a low gas flow of 2 l/minute. In all remaining combinations of flow and temperature optimum performance with a relative humidity range between 98 and 100% was obtained.

TEMPERATURE

At a system temperature setpoint of 34°C the temperature measured near the endotracheal tube varied between 33 and 35°C (table). The temperature was >0·5°C higher than the set value at high incubator temperature (37°C) and low flow (2 l/minute). It was >0·5°C lower than the set value at medium and high flow (6 and 16 l/minute) and at an incubator temperature of 35°C. At a set temperature of 37°C the respiratory gas temperatures near the endotracheal tube were between 35 and 37°C (table). The set temperature of 37°C was actually achieved in only one measurement combination (incubator temperature 34°C, flow 6 l/minute). The highest temperature drop of 2°C was observed with a cool incubator (34°C) and low gas flow (2 l/minute).

ABSOLUTE AIR HUMIDITY

The absolute inspired air humidity was, even under unfavourable conditions of cold respiratory gases (33–33·5°C), with 32–33 mg water/l air, above the recommended international standard.[2] At a set air temperature of 37°C the absolute humidity (38–43·5 mg/l) was clearly above this minimum standard (table).

CONDENSATION

Significant condensation inside the system was not detected in the parts installed inside the incubator. It was not necessary to install a water trap inside the inspiratory hose. Condensation was produced only in the expiratory hose outside the incubator.

FUNCTIONING OF THE MODULES

In some cases, the humidification modules had to be replaced within the first 24 to 48 hours of operating time because of a gradual drop in performance with inadequate relative air humidity. This was not indicated by the alarm system. According to the manufacturers another type of module is now used which has good performance for periods of at least one week. For hygienic safety it is recommended that the humidification modules should be replaced every 48 hours. Movability of the system is slightly restricted by the support inside the incubator.

Discussion

Relatively independently of the ambient conditions, air inspired through the nose is heated to body temperature in the lower respiratory tract after having passed the mucous membranes, reaching full water vapour saturation in the alveoli.[3] In artificial ventilation of newborn infants the most common method of humidification of inspiratory gas is vaporisation of water. The performance of the devices used varies considerably according to the functional principle and the type of instrument. In some there is a risk of overheating of the inspired air, especially when a drained nebuliser chamber is refilled with water. If, on the other hand, respiratory gases cannot be sufficiently warmed up the air capacity will not be sufficient to obtain a high absolute humidity in the respiratory tract. If heating filaments are used or in the situation of low flow and high incubator temperature the respiratory gases may actually be heated sufficiently. However, the air humidity might be low as the primary water load in an insufficiently heated nebuliser chamber is too low.[4]

According to our investigations the membrane humidification seems to fulfil the requirements with respect to constantly high respiratory gas temperatures and high air humidity even when the ambient temperature and the ventilator settings are changed. At a low gas temperature setpoint of 34°C the minimum standard[2] for the absolute air humidity in respiratory gases (30 mg water/l air) was reached in all measurement combinations. With high respiratory gas temperatures at a setpoint temperature at 37°C these concentrations were exceeded in all measurements, in some cases considerably. No significant amount of condensation is formed when the module is installed inside the incubator. The function of the hollow fibre net as a bacterial filter offers additional safety in hygiene. At the moment, the humidifier module must be replaced after 48 hours. One of the limitations of this system and of any humidification system that does not monitor inspired gas humidity is the fact that a gradual drop in performance might not be recognised.[4] A breakdown of the device would only be indicated by an alarm if the inspired gas temperature drops or if the pumping system is not working properly.

Inspired gas humidity cannot be predicted reliably from humidifier temperature.[5]

CLINICAL RELEVANCY

According to a study by Tarnow-Mordi *et al* a lower pneumothorax rate and less distinct chronic pulmonary changes were observed in ventilated premature babies with birth weights below 1500 g at higher respiratory gas temperatures, and thus probably at higher absolute air humidity, compared with another control group.[6] This seems plausible if results of animal tests and clinical studies are examined; these reveal a series of problems secondary to insufficient humidifier performance. Besides the risk of secretion retention,[7] infection,[8] development of atelectasis and impairment of diffusion[9] especially disturbances of the ciliary activity,[10] morphological changes in the tracheobronchial epithelium[11] were emphasised. By means of the membrane humidification as well as other improved devices, premature infants can now be ventilated with concentrations of absolute air humidity that lie clearly above the minimum international standard.[2] It is conceivable that excessive inspired gas humidification may be detrimental because too much heat and water could be adminstered to the patient.[8 12] One consequence could be that lower values of absolute humidity may be preferable to the consistently high concentrations we have documented at an Aquamod temperature setting of 37°C.

By means of controlled prospective studies that deal with the importance of different inspiratory gas temperatures and different inspired air humidity the optimum physical conditions in respiratory care of newborn infants should be investigated.

We thank Dräger for lending the equipment used in the study.

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Randomised controlled trial of colloid infusions in hypotensive preterm infants

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Abstract

Colloid infusions are often given to treat hypotension in preterm infants. The aim of this work was to assess whether it was the amount of protein or the volume of the colloid infused which accounted for the observed increase in blood pressure. Sixty preterm infants were randomised (20 in each group) to receive 5 ml/kg 20% albumin, 15 ml/kg fresh frozen plasma, or 15 ml/kg 4·5% albumin. All infusions were given at a rate of 5 ml/kg/hour in addition to maintenance fluids. The infants were randomised when hypotensive (systolic blood pressure less than 40 mm Hg for two hours). There was no significant difference in the blood pressure of the three groups before or one hour after beginning the infusion. The mean increase in blood pressure one hour after completing the infusion, however, was significantly lower in infants receiving 20% albumin: 9% compared with 17% in the group receiving 4·5% albumin, and 19% in the group receiving fresh frozen plasma. It is concluded that the volume infused rather than albumin load is important in producing a sustained increase in blood pressure.

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Colloid infusions are often used to treat hypotension in sick preterm infants. This hypotension may result from hypovolaemia due to fluid losses via the kidney and skin and increased leakage from capillaries in the lungs, or from myocardial depression due to asphyxia or hypoxia and resulting poor cardiac output. In the latter instance it seems preferable to avoid a large fluid load, but there are no data available to assess whether the improvement in blood pressure is the result of the protein or of the volume load infused. The aim of this study, therefore, was to compare the effects of colloid infusions of different volumes and protein content on blood pressure levels in hypotensive preterm infants and thus to determine the most efficacious type of colloid infusion.

Subjects and methods

Consecutive preterm infants were entered into the randomised trial when hypotensive but not overloaded with fluid. Hypotension was defined as a systolic blood pressure less than 40 mm Hg for two successive hours. None of the infants had clinical evidence of fluid overload. They were randomised by drawing a sealed envelope which instructed that they should receive one of three treatments: 5 ml/kg 20% albumin (200 g/l albumin—that is, 1 g/kg of albumin), or 15 ml/kg fresh frozen plasma (total protein 80 g/l, albumin 50 g/l—that is, 2 g/kg of protein or 0·75 g/kg of albumin), or 15 ml/kg 4·5% albumin (45 g/l albumin—that is, 0·675 g/kg of albumin). All infusions were given at a rate of 5 ml/kg/hour in addition to maintenance fluids. Thus the 20% albumin infusion was completed in one hour, but the other two infusions only after three hours. Systolic blood pressure was measured one hour after beginning the infusion and one hour after completing the infusion, and also four hours after beginning the infusions (that is, one hour after completing fresh frozen plasma and 4·5% albumin infusion, but three hours after completing the 20% albumin infusion).

Systolic blood pressure was measured either from an indwelling arterial catheter sited for clinical purposes or using a non-invasive Doppler method. All blood pressure measurements were made with the infant in the supine position. Measurements were not made if the infants had been recently handled, were crying, or were feeding.

Arterial cannulation was attempted on all admissions to the neonatal intensive care unit if the infant's oxygen requirements were in excess of 40% for six hours or the infant had a birth weight of less than 1000 g and was dependent on a ventilator. The unit's routine policy was first to attempt cannulation of the umbilical artery with a 4 or 5 French gauge catheter and if this was unsuccessful a peripheral artery was cannulated with a 24 or 26 French gauge cannula. Once arterial access was gained, blood pressure monitoring was begun. The arterial line was connected to a transducer (Medex Accuflush) and thence to a continuous monitor (Horizon 2000 monitor, Mennen). This gives a continuous display of the arterial waveform and minute by minute changes in the diastolic and systolic blood pressure. The arterial waveform was considered damped if the dicrotic notch was absent[1] and if there was less than a 10 mm Hg difference between the systolic and diastolic blood pressure. Only the results of non-damped systolic blood pressure measurements were used for this study. Measurements were recorded over a 10 minute period and the mean of the results was calculated.

A Doppler technique was used for blood pressure measurement in those infants with-

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out an arterial line in situ. An appropriately sized[2] cuff (Tricomed) was placed over the infant's upper arm. A coupling gel was applied over the brachial artery and the Doppler transducer (Ultrasonic Doppler flow detector) applied to this area. The operating frequencies of the transducer were from 8 to 9·7 MHz. The cuff was slowly inflated manually using a portable Accoson sphygmomanometer and then released until arterial pulsations were audible. The systolic pressure is the first signal heard. Three measurements were made on each occasion and the systolic blood pressure was expressed as the mean of these results. No infant required a change in blood pressure measurement technique during the study.

STATISTICAL ANALYSIS

The blood pressure immediately before beginning the colloid infusion was taken as the baseline blood pressure. The change in blood pressure from the baseline one hour after beginning, one hour after completing, and four hours after beginning the infusion was expressed as a percentage of the baseline blood pressure. Differences between the three groups were assessed for statistical significance using the Wilcoxon rank sum test.

Table 1 Patient characteristics. Results given are median (range) values

	Patient group		
	4·5% Albumin	*Fresh frozen plasma*	*20% Albumin*
Gestational age (weeks)	27 (24–35)	26 (23–34)	26 (23–34)
Birth weight (g)	844 (690–1954)	958 (566–1880)	860 (552–1800)
Length of ventilation (days)	14 (6–41)	14 (1–55)	12 (3–55)
Postnatal age (days)	2 (1–4)	2 (1–3)	2 (1–4)

Table 2 Systolic blood pressure and colloid infusions. Results given as median (range) values in mm Hg

	Patient group		
	4·5% Albumin	*Fresh frozen plasma*	*20% Albumin*
Baseline	31 (22–38)	35 (26–39)	31 (25–39)
One hour after beginning the infusions	38 (25–45)	38 (28–57)	38 (21–44)
One hour after completing the infusions	39 (27–46)	41 (29–51)	37 (25–55)
Four hours after beginning the infusions	39† (19–46)	41* (29–51)	34*† (25–42)

*$p<0{\cdot}05$
†$p<0{\cdot}01$

Table 3 Change in systolic blood pressure and colloid infusions. Results given as median (range) values of percentage baseline blood pressure

	Patient group		
	4·5% Albumin	*Fresh frozen plasma*	*20% Albumin*
Increase one hour after beginning the infusions	15 (−24 to 45)	8 (−10 to 90)	7 (−19 to 46)
Increase one hour after completing the infusions	22*(−17 to 58)	19* (−22 to 77)	9* (−15 to 50)
Increase four hours after beginning the infusions	22† (−17 to 58)	19† (−22 to 77)	5† (−18 to 53)

*$p<0{\cdot}05$.
†$p<0{\cdot}01$.

TRIAL SIZE

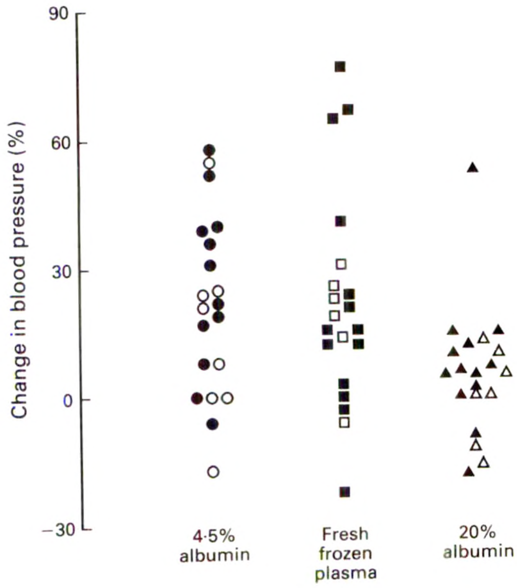
Using the results derived from 20 infants previously treated on our unit for hypotension with a colloid infusion we calculated that it would be necessary to randomise 60 infants (20 in each group) to detect with 80% power at the 5% level a significant difference of 10% in the change in blood pressure between the groups.

PATIENTS

Sixty patients were recruited into the study, 20 infants in each group. Table 1 shows that there was no significant difference in the gestational age, birth weight, length of ventilation, or postnatal age between the three groups.

Results

There was no significant difference in the blood pressure of the three groups at entry to the trial or after one hour of beginning or completing the colloid infusions. At four hours after beginning the infusion—that is, three hours after completing the 20% albumin infusion, the blood pressure of that group was significantly lower than that of the 4·5% albumin and the fresh frozen plasma groups ($p<0{\cdot}05$, $p<0{\cdot}01$, respectively) (table 2). The median increase in blood pressure one hour after beginning the colloid infusions tended to be greatest in those infants who had received 4·5% albumin. The increase in blood pressure one hour after completing the infusions was significantly greater in the infants who had received 4·5% albumin or fresh frozen plasma compared with those who had received 20% albumin ($p<0{\cdot}05$). This difference in the increase in blood pressure was even more marked ($p<0{\cdot}01$) when the three groups were compared at four hours after beginning the infusion (table 3, figure).



Change in blood pressure four hours after beginning the infusion. The change in blood pressure is expressed as a percentage of the baseline. Individual data shown (closed symbols indicate measurements made by the Doppler technique).

Discussion

Hypotension was recorded using systolic blood pressure measurements either made directly from an indwelling arterial catheter or by using a Doppler technique. The direct arterial blood pressure results were obtained from either umbilical or peripheral arterial cannulae. We felt it reasonable to pool the results from these different sites as an earlier study[3] had shown a good correlation between blood pressure measurements obtained from peripheral and umbilical cannulae. In addition, using such an approach we had previously recorded[4] arterial blood pressure results similar to those reported.[2] In those infants who were without arterial lines or in whom the arterial waveform was damped, blood pressure was measured using a Doppler transducer. It has been suggested that the Doppler technique may yield inaccurate results in sick preterm infants[5]; this has not been our experience.[4] We have previously shown that Doppler systolic blood pressure measurements have a high correlation (r=0·96) with arterial results.[4] The mean of the difference of paired measurements made by the Doppler technique and from an arterial catheter in 44 infants was less than or equal to 0·8 mm Hg from days one to seven.[4] Oscillometry has been a more popular non-invasive method of blood pressure monitoring than the Doppler technique.[6] We chose not to use that method, however, for although it seems accurate in older infants and children[6] it consistently under records the systolic and diastolic blood pressures of hypotensive very low birthweight infants.[7]

Although our study population were all very young, in a proportion it was not possible to make invasive arterial measurements. This was predictable from our earlier trial, which found by day four that 20% of infants no longer had an arterial catheter in situ and of those who did, a further 20% had a damped waveform.[4] There was, however, no significant difference in the number of infants in each group in whom blood pressure was measured using the Doppler technique. In addition, as our study period was of only four hours duration, we did not need to change our measurement technique in any infant, thus eliminating a further source of bias.

Infants were regarded as hypotensive if their systolic blood pressure was less than 40 mm Hg. This level was used as this is our routine clinical practice and has also been previously recommended.[8] This level may be inappropriate for the most immature infants included in our study, but there is little normative data available for such infants on which to base a more accurate diagnosis of hypotension. As there was no significant difference in the median or range of gestational age between our three groups, our use of a single level of blood pressure on which to diagnose hypotension in unlikely to have biased our results. Other studies[9 10] have used the mean rather than the systolic level, as it was felt to be more accurate than the systolic blood pressure which could be affected by damping. In this study we avoided this possible source of error by using only arterial measurements which were taken from an undamped arterial waveform. We felt it important to use systolic blood pressure levels as these can be measured in all infants regardless of the presence of an arterial line.

Albumin infusion has previously been associated with a reduction of tissue oedema, as evidenced by considerable weight loss.[11] There is the theoretical concern that by increasing blood volume it might prolong the patency of the ductus arteriosus.[12] In only one study has its use been associated with pulmonary oedema[13] and this did not occur in three other studies.[11 13 14]

Several groups have reported that albumin infusion increases blood pressure.[13–15] The effects previously recorded, however, were small and transient. Compared with the present trial, a smaller amount of albumin and smaller volume of fluid was infused in all three studies.[13–15]

The present results suggest that the volume rather than just the total amount of protein given is more effective in producing a sustained increase in blood pressure. The larger volumes of fluid were given at the same rate and hence over a longer period of time. The prolonged infusion of protein may also have had a greater effect by producing a sustained increase in oncotic pressure. Administration by such a method may have resulted in less protein loss from the circulation,[16] as the increase in albumin concentration would be expected to be smaller,[15] thus resulting in a lower diffusion gradient. This hypothesis is supported by our finding of a significantly lower blood pressure in the 20% albumin group compared with the other two groups at the same time after beginning the infusion (table 2).

There was no significant difference between the three groups in the blood pressure levels or change in blood pressure one hour after beginning the infusions. At that early stage all of the infants had received the same volume of fluid related to body weight (5 ml/kg/hour), but those receiving 20% albumin had been given a greater protein load. This further suggests that the volume of the fluid rather than protein load alone is responsible for the major effect on blood pressure.

We conclude that it is not only the amount of protein administered but also the volume of the vehicle infused that is important in producing a sustained increase in blood pressure in hypotensive preterm infants.

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Cardiac tumours in intrauterine life

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Abstract

Since 1980, 11 examples of cardiac tumour have been detected in the fetus out of a total of 794 congenital cardiac malformations. Patients were referred because of fetal hydrops in two, a family history of tuberous sclerosis in two, and because of the detection of a tumour mass during a scan at the local hospital in seven. The gestational age range at presentation was from 20–34 weeks. Of eight fetuses where death occurred, the histological type was rhabdomyoma in seven and teratoma in one. In seven cases, the lesion appeared single and in four there were multiple tumours. In two of the cases of rhabdomyoma, other family members had evidence of tuberous sclerosis. Termination of pregnancy took place in four cases; of seven continuing pregnancies, spontaneous intrauterine death occurred in four, and three children are still alive. Two of the three survivors has the clinical picture of tuberous sclerosis. The last case is as yet only 1 month old.

In summary, even where the lesion is single, the most likely diagnosis in fetal cardiac tumour is rhabdomyoma, with associated tuberous sclerosis. However, the characteristic features of this latter condition may not become evident until some months after birth.

(*Arch Dis Child* 1992;**67**:1189–92)

Cardiac tumours are rare in infants and children and are reported in 0·08% of children presenting to a paediatric cardiac referral centre[1] and between 0·0017% and 0·25% of a necropsy series.[2 3] Of 444 primary tumours reported by McAllister and Fenoglio, the most frequent histological type was rhabdomyoma, occurring up to three times more frequently than teratoma and fibroma in infants. Myxomas were found rarely in children but not seen in infants. The first case reports of the detection of a cardiac tumour in prenatal life were published in 1983, using M mode and cross sectional echocardiography, to diagnose a teratoma and a rhabdomyoma respectively.[4 5] Since then several case reports have appeared in the literature.[6–8] Since 1980 we have seen 11 examples of cardiac tumours in fetal life. We have studied the presentation, the type, and outcome of these cases.

Subjects and methods

From a series of over 10 000 fetal scans, heart disease was detected prenatally in 794. Of these, 11 fetuses had cardiac tumours. Intrapulmonary tumours were also found but differentiated from cardiac tumours by their position outside the pericardial cavity. Two fetuses were referred because of the detection of fetal hydrops, and two because of a family history of tuberous sclerosis. The remaining seven patients were referred because the tumour was suspected at the local hospital scan. In two patients, the diagnosis was made by sending a videotape of the scan recorded at the referral hospital. Patients were scanned using an Advanced Technical Laboratories Mark 3 or latterly Mark 4, and/or a Hewlett Packard 77020A phased array with colour flow mapping facility. Each videotape recording was examined retrospectively. The following features were noted: the presence of hydrops fetalis; the morphology and characteristics of the tumour; whether it was single or multiple; the position, and the presence or potential for obstruction to intracardiac flow. In four patients, successive examinations were performed during pregnancy. Any change in tumour characteristics were recorded. The outcome of each pregnancy was determined. In the eight fetuses in whom postmortem examination took place, the characteristics of the tumour were compared with the echocardiographic findings and histology obtained. The clinical findings in the three survivors were obtained.

Results

In one case, scanned initially at 18 weeks' gestation for a family history of cardiac tumour, a normal scan was found. On rescan at 22 weeks' gestation, tumours were clearly seen. Two fetuses were hydropic on referral and two

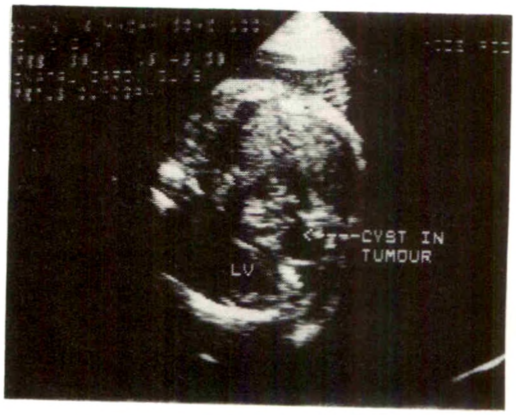

Figure 1 This shows a four chamber view of the heart. The large cystic tumour compressing the right ventricle proved to be a teratoma LV, left ventricle.

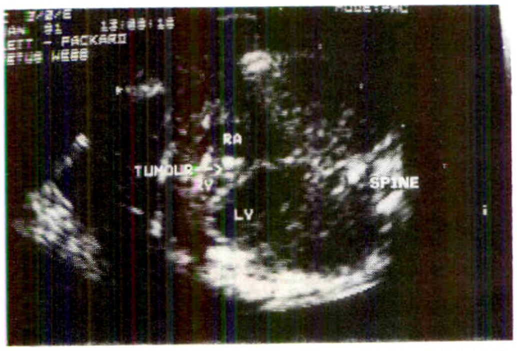

Figure 2 *Four chamber echocardiographic view of a fetal heart illustrating the presence of a rhabdomyoma in the wall of the right ventricle, which extended into the infundibulum. RV, right ventricle; RA, right atrium; LV, left ventricle.*

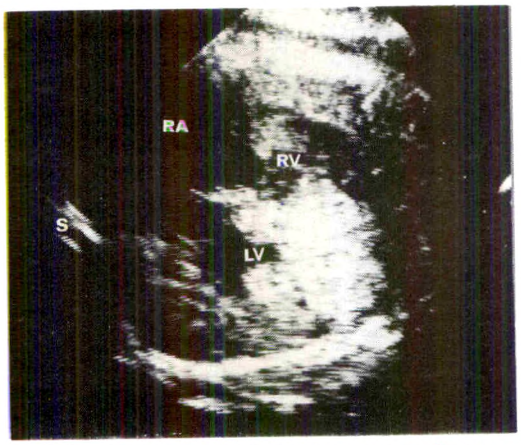

Figure 3 *This shows multiple rhabdomyomas on the four chamber view, with the right ventricular cavity (RV) almost obliterated by the tumour mass. RA, right atrium; LV, left ventricle; S, spine.*

became hydropic as pregnancy advanced. All but one of the 11 cases were solid tumours. The remaining case was intrapericardial in site and cystic in nature (fig 1), and a pericardial effusion developed with advancing gestation. Seven tumours were single (fig 2), including the one cystic lesion, and four were multiple (fig 3). Of the six solid single tumours, one was obstructing the mitral valve, one obstructing the tricuspid valve and pulmonary outflow tract, and the remainder involved the ventricular septum. Of these four septal tumours, one was causing fetal hydrops at the first study, one was potentially obstructive but the pregnancy was interrupted; two were not obstructive to blood flow and remained non-obstructive as pregnancy advanced.

OUTCOME

Of the cases with multiple tumours, two sought termination, one case survives but the tumours have not become obstructive, and the remaining case resulted in spontaneous intrauterine death. This last case showed increasing tumour size and increasing left ventricular outflow tract obstruction with advancing gestation. Episodes of supraventricular tachycardia were also noted before fetal death. One other patient in our series was documented to show episodes of intermittent tachycardia.

In four patients, termination of pregnancy was requested by the parents after discussion of the outlook and likely underlying disease. One of the four had a severely handicapped older child with tuberous sclerosis, and a further patient had right heart obstruction with atresia and hypoplasia of the pulmonary artery. Spontaneous intrauterine death occurred in four, three of whom presented with or developed fetal hydrops.

Postmortem examination was performed in all eight fetuses who died. The echocardiographic features were confirmed in all cases, in particular the multicystic nature of the pericardial tumour (figs 4–6). The histology in seven cases proved to be that of a rhabdomyoma and was pathognomonic in all cases. The cystic tumour proved to be a teratoma. Three patients

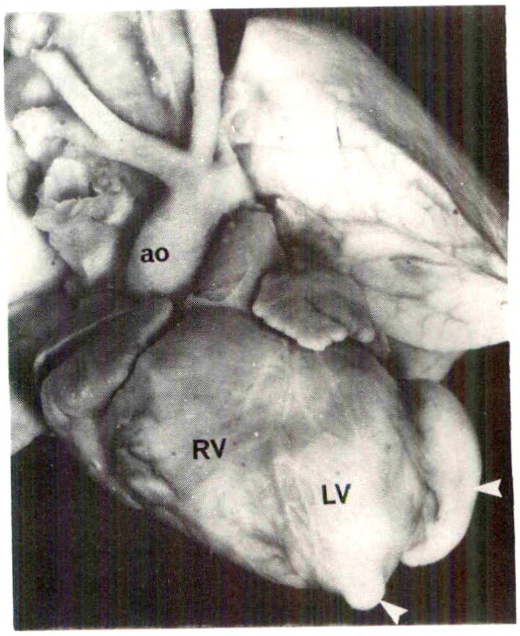

Figure 4 *This shows the pathological specimen in one of the cases of rhabdomyoma. Two tumours can be seen protruding from the wall of the left ventricle (V, arrows). Ao, aorta; RV, right ventricle.*

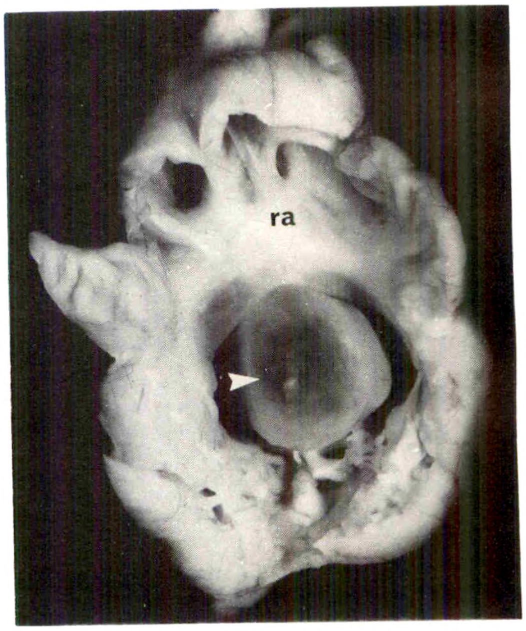

Figure 5 *The fetal heart opened at postmortem examination demonstrates a rhabdomyoma (ra) attached to and obstructing the orifice of the tricuspid valve (arrow). This correlated well with echocardiographic appearance.*

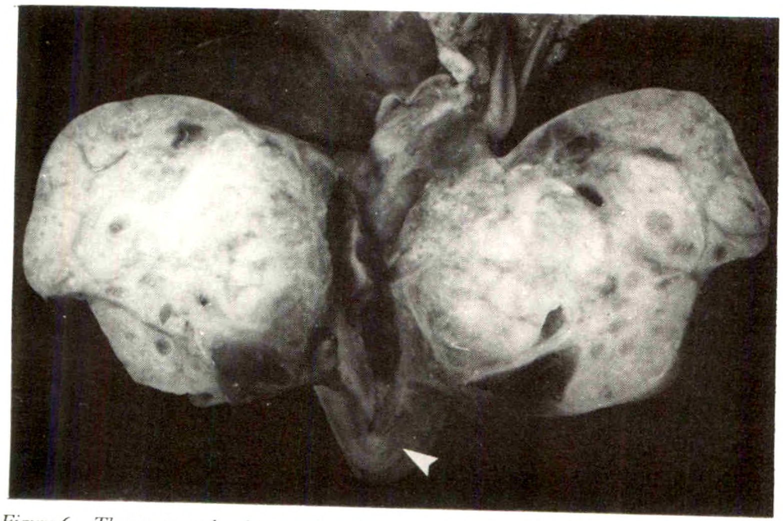

Figure 6 The teratoma has been sectioned to show the varying density of tissue and cystic areas, which correlated well with the echocardigraphic findings. The right ventricle is arrowed.

remain alive. Two (now aged 5 years and 16 months respectively) have developed the classic signs and symptoms of tuberous sclerosis. The last survivor is at present only 1 month old.

Discussion

Cardiac tumours were detected in this series more frequently than is reported in necropsy series, but less frequently than in a clinical study of children seen in a paediatric referral centre. This last is surprising as there was a high rate of intrauterine death—in four of seven continuing pregnancies (57%), the fetus died spontaneously. Death appeared to be caused by obstruction to blood flow and fetal hydrops in three, a widely reported association.[9 10] Structural heart disease has been described in previous cases.[11 12] In our case, tricuspid incompetence and pulmonary outflow obstruction appeared to be direct consequences of tumour growth rather than primary malformation. In another case, an increasing aortic velocity on sequential Doppler examination suggested increasing left ventricular outflow tract obstruction. In this case, spontaneous intrauterine death occurred but episodes of tachycardia had been noted before fetal death and this has been reported to be the cause of death in childhood[13] and in fetal life.[14] The mechanism for this is unknown but would appear to be secondary to disruption of the conducting tissue by the tumour or tumours, positioned in the intraventricular septum. The rhabdomyomas are well circumscribed macroscopically and microscopically and it is unlikely that their high glycogen content acts as a substrate for re-entry tachycardias.

In one case in our series tumours developed, in terms of echocardiographic detection, between 18 and 22 weeks' gestation; this illustrates the importance of sequential examination throughout pregnancy in mothers at high risk of rhabdomyoma in the fetus. Other authors have also reported tumours becoming evident as pregnancy progressed.[15] Of the two other cases of rhabdomyoma studied sequentially, the tumours increased in size in one and remained the same in the other. There is no evidence of regression during intrauterine life and maternal hormones have been implicated in their development and in postnatal regression. The teratoma increased strikingly in size between 20 weeks and intrauterine death at 30 weeks' gestation. The echocardiographic appearance of the cystic nature of this tumour and its epicardial position were characteristic of teratoma and contrasted with the appearance of the more commonly occurring rhabdomyomas, none of which were cystic and all of which were intracardiac. The tumours in all our surviving cases have regressed in postnatal life, which is consistent with previous reports.[8 16]

The histological findings are consistent with previous reports and with the findings in children, in that rhabdomyoma was much the most common histological type of tumour. Rhabdomyomas are associated with tuberous sclerosis in between 50% and 78% of cases, according to different authors.[1 8] In none of the fetal necropsy specimens was evidence of tuberous sclerosis found elsewhere in the fetus despite the presence of proved tuberous sclerosis in one parent in each of two cases. Of the three surviving neonates, one developed the clinical features of tuberous sclerosis at 6 months of age and the second at almost 1 year of age. The remaining neonate is only 1 month old at present but we feel is highly likely to develop the picture of tuberous sclerosis in later infancy. This would suggest that apart from rhabdomyoma, the other signs of tuberous sclerosis are rarely found in fetal life or early infancy, although this will be the underlying diagnosis eventually.

The severity of the clinical picture, particularly of fits and developmental delay, although usually associated with significant handicap, can be variable.One of our affected parents had never had fits and was of normal intelligence. Similarly, family studies in cases of children with tuberous sclerosis have revealed unsuspected affected parents.[6 17 18] A family history of tuberous sclerosis is an unusual cause of referral to our unit. A total of five patients have been referred for this reason in 11 years, including the two which proved positive. Part of the explanation for this may be that the absence of cardiac tumours in the fetus does not guarantee absence of the disease. Geva *et al* suggested that intrauterine surgery for an obstructive cardiac rhabdomyoma might be beneficial and that a normal necropsy excludes tuberous sclerosis.[13] Our results indicate that this is not so and we do not feel that such treatment should be offered.

Despite the location of the gene for tuberous sclerosis on chromosome 9, multiple loci are suspected and diagnosis by gene mapping is not yet available. In view of this, and the spontaneous mutation rate of at least 60%,[19] echocardiographic examination of the high risk pregnancy for cardiac tumours may be the only method of detecting an affected fetus in the immediate future. However, the absence of cardiac tumours in a high risk fetus will not exclude the diagnosis of tuberous sclerosis.

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Changes in the plasma aminogram of parenterally fed infants treated with dexamethasone for bronchopulmonary dysplasia

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Abstract

A substantial increase in the plasma concentration of most amino acids was observed in 59 preterm infants with chronic lung disease soon after the initiation of dexamethasone therapy. The size of increase appeared to be dose related. This phenomenon is likely to be the result of steroid induced protein catabolism. Interestingly, neither phenylalanine nor tyrosine concentrations were significantly increased.

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Dexamethosone is now often used in the treatment of bronchopulmonary dysplasia (BPD).[1–4] Corticosteroid therapy is associated with many serious complications which have yet to be thoroughly and systematically examined in preterm infants. Since the decision to prescribe dexamethasone will depend on the clinician's perception of the risks and benefits of the treatment, there is an urgent need to establish and to document any undesirable effects as accurately and comprehensively as possible.

An important side effect of corticosteroids is an increase in resting metabolic expenditure and urinary nitrogen loss due to promotion of protein catabolism.[5–7] We have previously reported a marked rise in blood urea concentration in dexamethasone treated babies secondary to structural protein breakdown.[8] As the breakdown of protein releases amino acids, one aspect of this effect of steroids might be to cause hyperaminoacidaemia, especially in babies already receiving an amino acid solution parenterally. In view of the potentially toxic effect of some amino acids, notably, but not exclusively, phenylalanine, we monitored the plasma aminogram in parenterally fed preterm infants before and during dexamethasone treatment for BPD.

Patients and methods

Over a four year period between January 1987 and December 1990, 59 parenterally fed preterm infants who received dexamethasone for BPD were studied. Their clinical characteristics and the severity of their chronic lung disease, as reflected by the duration of intermittent positive pressure ventilation and oxygen dependency, are summarised in table 1.

Steroids were started at a mean (SD) postnatal age of 20 (9) days. In all cases, a three week course of dexamethasone was given, starting at 0·6 mg/kg/day, reducing to 0·3 mg/kg/day in the second week and to 0·15 mg/kg/day in the third week. All babies who entered the trial were on total parenteral nutrition. The regimen of the unit was to start all ventilated preterm babies on parenteral nutrition on the second day of life with 0·5 g/kg/day of Vamin 9 glucose, 0·5 g/kg/day of Intralipid 20% (KabiVitrum) and 10% dextrose, plus electrolytes, trace minerals, and vitamins. In the absence of contraindications such as severe jaundice, metabolic acidosis or sepsis, amino acid and fat intakes were increased daily by increments of 0·5 g/kg, to a maximum of 3 and 3·5 g/kg/day of amino acid and lipid respectively. All nutrients were infused at a constant rate throughout the 24 hour period. Daily fluid intake was increased according to estimated fluid requirements and carbohydrate tolerance, usually reaching the maximum level of 180 ml/kg/day on day 7. Thereafter, these rates of fluid and nutrient intake were maintained throughout the whole study period (one week before and during the three weeks of steroid treatment) to ensure constant protein and energy intake until mechanical ventilatory support was discontinued and the baby was well enough to tolerate enteral milk feeds.

Table 1 The clinical characteristics of the 59 babies

Clinical characteristics	*Mean (SD)*
Gestational age (weeks)	27 (2)
Birth weight (g)	1026 (298)
Postnatal age when dexamethasone started (days)	20 (9)
No of days on assisted ventilation	26 (13)
No of days dependent on supplementary oxygen	57 (320
No of days in hospital	102 (43)

Plasma aminograms were checked at weekly intervals as long as the babies were on parental nutrition. Amino acid analysis was carried out on a Hilger Chromaspeck automated ion exchange amino acid analyser. The chemical pathology laboratory participated in the external quality control system (NEQUAS) operated by the Wolfson Research Laboratory, Queen Elizabeth Medical Centre, Birmingham.

Statistical comparisons between sets of parametric data were performed using the Student's paired *t* test.

Results

The concentrations of 19 amino acids were measured. There were no significant differences between the pretreatment (week −1) concentrations and our previously published

Table 2 Mean plasma amino acids concentrations before dexamethasone treatment and mean change from base measurements during study (mmol/l)

Amio acid	*Week-1* *Mean (SE)*	*Week 1* *Change (SE)*	*Week 2* *Change (SE)*	*Week 3* *Change (SE)*
Aspaartic acid	61 (4)	+21 (5)**	+12 (6)	+7 (10)
Threonine	207 (13)	+66 (18)**	–24 (21)	–38 (18)
Serine	325 (17)	+178 (26)**	+93 (36)*	+51 (25
Glutamic acid	233 (14)	+87 (19)**	+53 (23)*	–4 (30)
Glutamine	518 (25)	+367 (42)**	+230 (32)**	+348 (33)**
Glycine	359 (14)	+163 (24)**	+54 (26)*	+41 (21)
Alanine	280 (14)	+263 (30)**	+221 (24)**	+163 (33)*
Cystine	48 (3)	+18 (5)**	+11 (4)*	+6 (5)
Valine	219 (8)	+68 (11)**	+35 (13)*	+20 (15)
Methionine	31 (2)	+24 (3)**	+12 (3)**	+10 (3)*
Isoleucine	64 (4)	+25 (4)**	+16 (6)**	+22 (8)*
Leucine	103 (4)	+42 (6)**	+29 (7)**	+25 (8)*
Tyrosine	330 (58)	–29 (68)	–176 (69)*	–198 (95)*
Phenylalanine	174 (11)	+22 (14)	–44 (16)*	–51 (21)*
Histidine	102 (3)	+34 (6)**	+23 (5)**	+8 (5)
Ornithine	212 (12)	+112 (12)**	+66 (12)**	+28 (11)*
Lysine	157 (11)	+132 (15)**	+82 (16)**	+29 (20)
Arginine	21 (2)	+24 (5)**	+19 (5)**	–2 (4)
Proline	376 (24)	+207 (28)**	+15 (32)	–54 (33)

Significant change *p<0·05; **p<0·01.

reference data.[9] Table 2 documents the change in plasma amino acid concentrations during the full study period from week –1 to week 3.

When the pretreatment plasma amino acid concentrations were compared with those in the first week of treatment, all except the aromatic amino acids, phenylalanine and tyrosine, showed a significant increase in concentration ($p<0.01$). During the second week of treatment, at half of the initial dexamethasone dose, most amino acid concentrations continued to be significantly raised ($p<0.05$). Three, however, returned to their pretreatment concentrations and they were aspartic acid, threonine, and proline. In the final week of steroid treatment, at a quarter of the original dose, most amino acid concentrations returned to their pretreatment concentration. Only glutamine, alanine, methionine, isoleucine, leucine, and ornithine concentrations were still significantly raised ($p<0.05$). Both the amino acids in the aromatic group showed a significant decrease in plasma concentration at week 3.

The overall percentage increase of the total plasma amino acid concentrations from the pretreatment value for weeks 1, 2, and 3 were 45%, 17%, and 5% respectively.

Discussion

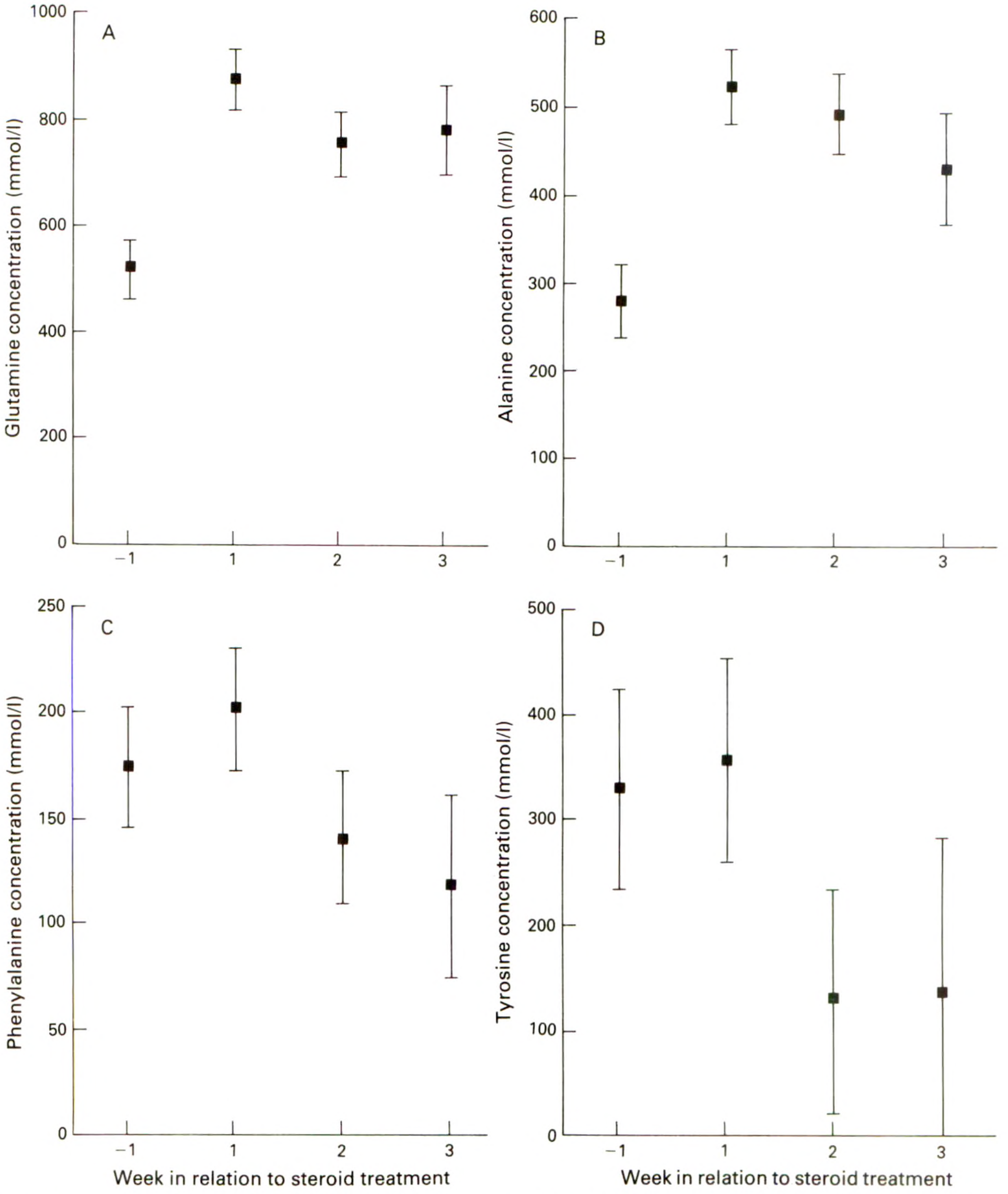
Dexamethasone belongs to the catabolic class of steroids and therapeutic doses of such drugs are known to induce hypermetabolism. They cause lipolysis and proteolysis,[10] enhance gluconeogenesis, and interfere with peripheral glucose uptake and utilisation.[10] We have recently reported enhanced protein catabolism in preterm infants given dexamethasone for the treatment of bronchopulmonary dysplasia.[8] We speculated that if structural proteins in the nervous system were involved, neurodevelopmental outcome might be prejudiced. As one of the complications of total parenteral nutrition in the newborn is an increase of plasma amino acid concentrations,[11–14] the amino acids released as a consequence of steroid induced structural protein breakdown in this group of infants could aggravate the risk of hyperaminoacidaemia and represent an additional threat to the integrity of the developing brain.

In this study, we have demonstrated a generalised and substantial increase in plasma concentration of almost all amino acids soon after starting dexamethasone therapy which is the result of steroid induced proteolysis. This effect appears to be dose related, and with the smallest dose of dexamethasone (0·15 mg/kg/day) in week 3, the majority of plasma amino acid concentrations have returned to their pretreatment values. The overall percentage increase in plasma concentration above the pretreatment value declined from 45% in the first week, to 17% in the second week, and to 5% in the third week. This dose related phenomenon has been well documented in renal transplant patients treated with corticosteroids.[7 15] It is, therefore, desirable to use the minimum dose of steroid compatible with effective anti-inflammatory action and to encourage a rapid tapering schedule to minimise the side effect of the treatment.

A possible alternative explanation for the fall in amino acid concentrations in weeks 2 and 3 is that the increased plasma amino acid concentrations of week 1 stimulate increased insulin production.[16] Insulin, which is well known to have an anabolic effect, could then lead to increased amino acid uptake by the tissues. Leucine, in particular, is known to exert an anabolic effect via increased insulin production.[17]

The largest and most sustained increases in concentration were seen for glutamine and alanine (figs A, B). This is consistent with an enhanced rate of protein catabolism and a subsequent increase in the rate of amino acid catabolism. Amino acids cannot be stored and those liberated by enhanced protein hydrolysis must be catabolised. The first step in the catabolism of all amino acids is a transamination reaction to α ketoglutarate or pyruvate yielding glutamate or alanine. Thus, when there is an enhanced flux of amino acids through the degradative pathways, one would expect to observe an increase in the concentration of the transamination intermediates alanine, glutamine, and glutamic acid.

An increased concentration of certain amino acids may have potential ill effects. In recent years, a series of correspondence in the *Lancet*[11–14] reported high plasma phenylalanine concentration in newborn infants on total parenteral nutrition exceeding the toxic limit of 600 mmol/l recommended for the treatment of phenylketonuria.[18] We were both surprised and reassured to find that neither phenylalanine nor tyrosine plasma concentrations increased significantly at any time during dexamethasone treatment. In fact the concentration of both aromatic amino acids decreased significantly in the final week of treatment when compared with their pretreatment control values (figs C, D). Moreover, we did not observe a single instance of either amino acid exceeding the toxic limit during the treatment period. The reason why this group of amino acids behaves differently from the others is uncertain. It may relate to the ability



Plasma concentrations before and during dexamethasone treatment (bars show 95% confidence intervals). (A) glutamine, (B) alanine, (C) phenylalanine, and (D) tyrosine.

of corticosteroids to stimulate the enzymatic activity of specific hepatic aminotransferase[10] and potentiate the removal of these amino acids from the circulation.

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Coagulation screening tests in high risk neonates: a prospective cohort study

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Abstract

Forty seven infants in a prospective cohort of 170 high risk neonates without signs of overt bleeding had abnormal coagulation screening tests within 36 hours of birth. Early thrombocytopenia was a better predictor of prolonged prothrombin times and hypofibrinogenaemia than very low birth weight, fetal growth retardation, or poor five minute Apgar scores.

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Although the occurrence of neonatal thrombocytopenia has been studied,[1] little is known about the prevalence of plasma clotting defects in unselected high risk infants. We therefore performed coagulation screening tests within 36 hours of birth in a prospective cohort of critically ill neonates. We also examined whether abnormalities of plasma coagulation can be predicted by early low platelet counts and several other generally accepted risk factors such as very low birth weight, fetal growth retardation, and low five minute Apgar scores.

Subjects and methods

SUBJECTS

The study was conducted in the neonatal intensive care unit at McMaster University between April 1989 and March 1990. All infants admitted to the unit were eligible for enrolment if the following two criteria were met: (i) postnatal age less than 36 hours and (ii) indwelling arterial catheter with undampened pressure tracing. The latter ensured recruitment of the group of patients in the nursery who were most ill and also allowed artifact free blood sampling. The study was approved by the Institutional Review Board for research involving human subjects.

The decision to place an arterial catheter for monitoring purposes was made by the attending medical staff without reference to this study. Patency of the catheter was maintained with an infusion of 5% dextrose containing 1 U/ml heparin at a rate of 1 ml/hour. All flushing solutions were heparin free. Apart from the administration of 24 U/day heparin, no study patient received anticoagulant or thrombolytic drugs. Vitamin K (0·5–1·0 mg) was given parenterally at birth to all infants. Administration of blood products during the six hours preceding the study sample was recorded in all subjects.

COAGULATION ASSAYS

Blood samples (0·9 ml) for coagulation studies were drawn once from the free flowing arterial catheter at the time of medically ordered sampling for complete blood counts. The prothrombin time was determined using human thromboplastin (Thromborel S, Behringwerke, Germany), and expressed as the international normalised ratio (INR)

$$\text{INR}=\left(\frac{\text{Patient prothrombin time}}{\text{Control prothrombin time}}\right)^{\text{ISI}}$$

where ISI is the international sensitivity index of the thromboplastin used in the local laboratory.[2] Fibrinogen was measured using the method of Clauss.[3] Platelet counts $<150\times10^9$/l, fibrinogen concentrations $<1\cdot5$ g/l, and an INR $>1\cdot5$ were considered abnormal in all study patients.[1 4] Plasma samples were shown to be free of heparin contamination by protamine titration.

ANALYSIS

Observed frequencies and 95% confidence intervals of laboratory abnormalities were determined. Sensitivities, specificities, predictive values, and likelihood ratios were calculated to assess whether birth weight <1500 g, gestational age <29 weeks, five minute Apgar scores <6, and platelet counts $<150\times10^9$/l predicted abnormalities of plasma coagulation.[5] As fetal growth retardation has been implicated as a risk factor of coagulopathy, the frequency of plasma coagulation defects was also examined in infants with birth weights below the tenth centile according to local population based standards.[6]

Results

STUDY INFANTS

During the 12 month study period, 191 infants fulfilled the two entry criteria, 177 of whom were entered into the study. Fourteen infants were either missed, or sampled after the first 36 hours of life. Seven blood samples were mislabelled or clotted. For ethical reasons the study protocol did not allow repeat samples to be drawn in these instances. Thus results are reported for 170 infants, or 89% of all potentially eligible infants. Table 1 summarises the

Table 1 Characteristics of the 170 infants studied

Gestational age (weeks)	29 (24–41)*
Birth weight (g)	1380 (600–5300)*
Sex (male/female)	93/77
In/outborn	123/47
5 minute Apgar score	7 (2–10)*
Postnatal age (hours)	16·6 (0·8–35·5)*
No with mechanical ventilation at time of study	144
No with fresh frozen plasma infusions before study	27

*Values are median (minimum–, maximum) values.

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important characteristics of the study group. No infant had received blood products for clinical bleeding before the coagulation screen. Twenty seven infants were given up to 20 ml/kg of fresh frozen plasma to improve hypovolaemia and hypotension during the six hours preceding the blood sample. Coagulation screening tests were entirely normal in 67% of patients who received plasma, compared with 63% of those who did not. Owing to the considerable overlap of the respective 95% confidence intervals (46·0 to 83·5% *v* 54·5 to 70·9%), the effect of the plasma infusions on the test results was not considered important enough to justify stratification of subsequent analyses according to plasma use.

ABNORMALITIES OF COAGULATION SCREENING TESTS

Table 2 gives the observed frequencies of abnormal tests together with the 95% confidence intervals. Of the 47 infants with abnormal plasma coagulation, 18 patients had an increased INR, whereas 16 subjects had a low fibrinogen concentration. In a further 13 infants the two tests were abnormal. Among infants with an abnormal INR, the median value was 1·7 (maximum 3·1). Among infants with hypofibrinogenaemia the median fibrinogen concentration was 1·1 g/l (minimum 0·3 g/l). The median platelet count in the 36 infants with thrombocytopenia was 118×10^9/l (minimum 36×10^9/l).

PREDICTION OF COAGULOPATHY

Table 3 summarises the sensitivities, specificities, predictive values, and likelihood ratios for all examined risk factors of coagulopathy.

Discussion

Abnormalities of the coagulation system are reported to be common in ill neonates, yet little is known about the prevalence of plasma clotting defects in unselected high risk infants. In this prospective cohort study coagulation screening tests were abnormal within the first 36 hours in about one third of all infants who were sick enough to require an indwelling arterial catheter for monitoring purposes. Abnormalities of plasma coagulation could not be predicted accurately by more readily known risk factors such as immaturity, fetal growth retardation, or poor Apgar scores. The strongest predictor of coagulopathy was thrombocytopenia. Infants with platelet counts $<150\times10^9$/l were 3·7 times more likely to have plasma coagulation defects than infants with normal platelet counts. Further, normal INR and fibrinogen values were less than half as likely to be found in infants weighing <1500 g than in larger infants. Low birth weight, however, was not a strong predictor of abnormal plasma coagulation. Thus our data suggest that screening for coagulopathy will have the highest yield in infants with early thrombocytopenia whereas infants with birth weights >1500 g are least likely to have laboratory evidence of coagulopathy.

The clinical significance of abnormal coagulation screening tests is currently uncertain. Although no infant was noted to bleed overtly at the time of the study, occult haemorrhage may well have contributed to the morbidity of these critically ill infants. This hypothesis is supported by previous descriptions of an association between abnormal coagulation tests and the presence and severity of intracranial haemorrhage in preterm infants.[7–10] Trials of fresh frozen plasma or other preparations of coagulation factors in the prevention of intracranial haemorrhage have yielded conflicting results.[11] Further studies are therefore required to determine whether sick newborn infants would benefit from the detection and correction of clinically inapparent clotting defects.

Table 2 Abnormalities of coagulation screening tests in 170 high risk neonates

Coagulation profile	*No (%) of occurrences*	*95% Confidence interval (%)*
Normal	108 (64)	55·8 to 70·8
Coagulopathy	26 (15)	10·2 to 21·6
Coagulopathy and thrombocytopenia	21 (12)	7·8 to 18·3
Thrombocytopenia	15 (9)	5·0 to 14·1

Table 3 Prediction of coagulopathy

Predictor	*Sensitivity (%)*	*Specificity (%)*	*Positive predictive value (%)*	*Negative predictive value (%)*	*Likelihood ratio*
Birth weight:					
<1500 g (n=97)	77		37		1·5
≥1500 g (n=73)		50		85	0·46
Gestational age:					
<29 weeks (n=64)	51		38		1·6
≥29 weeks (n=106)		67		78	0·73
Small for gestational age:					
Yes (n=20)	17		40		1·7
No (n=150)		90		74	0·92
Apgar score					
<6 (n=26)	22		38		1·6
≥6 (n=141)*		87		74	0·90
Platelet count:					
$<150\times10^9$/l (n=36)	45		58		3·7
$\geq150\times10^9$/l (n=134)		88		81	0·63

*Three missing values in infants not born in this hospital.

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Clinical application of urine antigen detection in early onset group B streptococcal disease

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Abstract

The aim of this study was to test the sensitivity and specificity of antigen detection for group B streptococcus (GBS) from the urine of neonates with early onset GBS sepsis. GBS sepsis was defined as early (<48 hours) signs of sepsis in a neonate colonised with GBS. Neonates of 26 weeks' gestation or more, considered at risk for sepsis, were prospectively investigated for one year. Investigations included culture of superficial swabs to assess colonisation, blood culture, and the Wellcogen Strep B latex particle agglutination test on urine. Of 188 neonates investigated, 17 (9%) had GBS sepsis. The urine antigen test had a sensitivity of 88% and specificity of 98%. The positive predictive value was 79% and the negative predictive value 99%. Blood culture was positive in only five neonates (29%). The annual incidence of GBS sepsis was 4·0 per 1000 and of blood culture positive GBS disease was 1·2 per 1000 live births. Three neonates died. The application of the urine antigen test of clinical neonatal practice is discussed.

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The currently accepted definition of early onset group B streptococcal disease is of a baby with clinical signs of infection, usually respiratory distress and a positive blood and/or cerebrospinal fluid (CSF) culture. However, Webber *et al* have described babies with early onset pneumonia caused by group B streptococcus (GBS) of whom only 46% had positive blood cultures.[1] The remaining 54% were heavily colonised with GBS. Their study did not evaluate urinary GBS antigen detection. Webber's study suggests that a definition requiring positive blood and/or CSF culture may underestimate the incidence of GBS sepsis.

The detection of GBS antigen by methods such as the latex particle agglutination (LPA) test have been studied. The theoretical advantages of this test, compared with traditional blood culture, include antigen detection in body fluids in concentrations as low as 60–70 ng/ml,[2] the detection of antigen even if prior antibiotic therapy has resulted in minimal live or even dead organisms, and the ability to test sequential urine specimens. Furthermore, once urine has been collected the test takes only 20 minutes to perform.

We have used antigen detection by the LPA method in babies with suspected sepsis and have examined the sensitivity and specificity of urine antigen detection for babies with positive blood culture, and for babies with a clinical diagnosis of GBS sepsis based on clinical signs and colonisation with GBS.

Methods

Neonates of 26 weeks' gestation or more considered at risk for sepsis entered the study prospectively for one year from November 1986 to October 1987 inclusive. They were considered at risk if one or more of the following criteria were fulfilled: positive antenatal genital swab for GBS, spontaneous onset of preterm labour, prolonged rupture of membranes (>12 hours), intrapartum fever (>37·5°C), fetal distress, birth asphyxia and/or any of the following occurring within 48 hours of birth—unexplained respiratory distress, sustained tachycardia (>160 beats/min), shock, temperature <36·5°C or >37·5°C. Microscopy and culture of ear and umbilical swabs and gastric aspirate, blood culture, and the Wellcogen Strep B LPA test were performed when indicated as soon after birth as practicable.

The Wellcogen Strep B LPA test is designed to detect polysaccharide wall antigen released from the GBS into various body fluids (for the purpose of this study urine was tested by bag collection after thorough cleansing of the skin). The test was used according to the manufacturer's instructions. That is, the urine was boiled for a minimum of five minutes, centrifuged for 10 minutes at 3000 rpm and one drop of supernatant tested against a control latex and one drop against a test latex. Agglutination, if present, was recorded after gently rocking the test card for three minutes.

In the neonates at risk of sepsis, early onset GBS disease was defined as either clinical signs (unexplained respiratory distress, sustained tachycardia >160 beats/min, shock, temperature <36·5°C or >37·5°C within 48 hours of birth) in a baby colonised by GBS, or a positive blood culture before the onset of clinical signs (performed because of one or more of the antenatal risk factors). The absence of GBS disease was defined as either clinical signs in a non-colonised baby or no signs in a colonised baby.

From the at risk group of infants a subgroup of 100 neonates without disease were randomly selected in order to establish (a) the proportion of antenatal compared with postnatal risk factors and (b) the significance of the neutrophil count and placental histology.

The sensitivity, specificity, and positive and negative predictive values of the Wellcogen Strep B LPA test were calculated by applying the test results to the above definition of early onset GBS disease. The 95% confidence limits were calculated for the sensitivity and the specificity of the LPA test. Fisher's exact and χ^2 tests were used in the analysis of risk factors. The study was carried out at a time before the routine or widespread use of antenatal genital swabs for the detection of GBS and before the routine or widespread use of antibiotics in mothers (or babies) where antenatal risk factors for GBS infection were present. Nevertheless, some women were swabbed if there was prolonged rupture of the membranes (>12 hours) at term, preterm rupture of membranes, or intrapartum fever.

Results

There were 4282 live births during the one year study period. One hundred and eighty eight neonates with antenatal or postnatal risk factors for early infection were screened for sepsis using all three of the following tests: blood culture; surface swabs and/or gastric aspirate microscopy and culture; and urinary LPA test. Of the 17 neonates who had GBS disease, 16 were colonised with GBS and had clinical signs, and one was asymptomatic with a positive blood culture. The remaining 171 neonates did not have GBS disease.

The sensitivity, specificity, and positive and negative predictive values for the LPA test are shown in table 1. There were four false positive tests. Two occurred in babies colonised with GBS, one baby's mother had received intrapartum antibiotics, and the fourth was neither colonised nor had the mother received antibiotics. Five of the 17 neonates with GBS disease (29%, 95% confidence interval 7% to 51%) had blood cultures positive for GBS. One of these had no clinical signs of sepsis. All five neonates had a positive LPA test on urine. There were two false negative tests, both in neonates with clinical signs of sepsis and colonised with GBS. The mother of one of these babies had received intrapartum antibiotics. A repeat urine test was not performed in either baby.

Using the traditional definition of GBS sepsis, a positive blood (or CSF) culture in a neonate with clinical signs or one with maternal risk factors, the sensitivity of the LPA test is 5/5 (100%) and the specificity is 169/183 (92%).

Of the 12 neonates with positive LPA tests but negative blood cultures, 11 had an antenatal risk factor (including nine whose mothers had intrapartum fever >37·5°C).

Table 2 shows the number of neonates with and without early onset GBS disease, and the proportion that were preterm, neutropenic according to the criteria of Manroe *et al*,[3] and had placental chorioamnionitis or vasculitis as defined by Russell.[4] There was no statistical difference between the disease and the non-disease groups for preterm birth, neutropenia or for chorioamniotis/vasculitis, although the apparent trend was for babies with disease to have neutropenia.

Table 1 Sensitivity and specificity of the LPA test

	GBS disease	*No GBS disease*	*Total*
LPA test positive	15	4	19
LPA test negative	2	167	169
Total	17	171	188

Sensitivity, 88% (95% confidence interval 73% to 100%); specificity, 98% (95% confidence interval 96% to 100%); positive predictive value, 79%; negative predictive value, 99%.

Table 2 Early onset GBS disease: gestation, neutropenia, and chorioamnionitis/vasculitis. Results are number (%)

	GBS disease	*No GBS disease*
Preterm	10/17 (59%)	52/100 (52%)*
Neutropenia	4/17 (24%)	8/98 (8%)*
Chorioamnionitis or Vasculitis	9/14 (64%)	34/72 (47%)*

*No significant difference between disease and no disease groups.

The annual incidence of early onset GBS disease was four per 1000 live births. The annual incidence of blood or CSF culture positive GBS disease was 1·2 per 1000 live births. Three preterm neonates died as a result of the disease giving a case fatality rate of 17·7%.

Discussion

This study defined early onset GBS disease as the presence of clinical signs within 48 hours of birth in a neonate colonised by GBS, or positive blood or CSF culture. This definition is somewhat controversial. However, support for its validity is provided by our finding that 11 of 12 neonates with urinary GBS antigen detected in the face of negative blood cultures had recognised maternal risk factors for GBS sepsis. In order to detect GBS disease the urinary LPA test was applied to neonates who had either antenatal or postnatal risk factors for infection. The sensitivity of 88% and specificity of 98% for the LPA test in this study suggest a rapid means for presumptively diagnosing early onset GBS disease before formal cultures are available.

Previous studies have examined the sensitivity and specificity of the LPA test in detecting GBS sepsis.[2 5–11] Most have relied on positivity of blood or cerebrospinal fluid culture in order to define the sensitivity and specificity of the LPA test. The present study suggests blood culture is only 29% (5/17) sensitive (95% confidence interval 7% to 51%) in detecting early onset GBS disease.

The lack of specificity when judged by blood culture, creating false positive urinary LPA tests, has been addressed by several authors. Harris *et al* investigated neonates with suspected sepsis who had positive LPA tests and negative blood cultures.[12] These authors found that local contamination of the perirectal skin or urinary tract with B streptococcus was an unlikely source of false positive LPA reactions. They concluded that maternal antibiotic pretreatment during labour may represent an important cause of apparent false positive LPA reactions. False positive urine tests have been observed rarely in patients infected with other bacterial pathogens, for example *Proteus mirabilis*.[7]

Sanchez *et al* suggested that contamination of bag specimens of urine with GBS from heavy perineal and rectal colonisation may produce a positive urine LPA test in an infant with no systemic signs of infection.[13] Microbiological tests carried out at the Royal Prince Alfred Hospital, Sydney, suggested that heavy contamination with 10^7 organisms/ml or more of GBS was required to cause a 'false positive' LPA test (Dr R Benn, personal communication).

Ascher *et al* believe that the meaning of a positive urine antigen result with a concomitant negative blood culture remains unresolved, but suggest that gastric absorption of GBS antigen may play a part.[14]

As the negative predictive value of the LPA test is 99%, a negative result in an at risk infant who is asymptomatic can support a clinical decision not to treat with antibiotics. This presumes GBS disease is a leading cause of bacterial morbidity in the particular neonatal unit. While early antibiotic treatment is indicated in the neonate when there are clinical signs of sepsis, the decision to cease antibiotics is usually made on the basis of rapid clinical improvement in the absence of positive cultures. A negative LPA test provides additional evidence with which safely to terminate antibiotic treatment.

The annual incidence of early onset GBS disease in this study was 4 per 1000 live births, a rate that is within the reported range in the literature but is higher than recent reports for the USA and Europe.[15] This figure was threefold greater than the annual incidence of 1·2 per 1000 live births as determined by blood culture over the same period of time in the present study. The definition of early onset GBS disease used in this study may result in overdiagnosis. It is, however, clinically safer than relying on blood culture which underestimates the disease at least twofold.[1]

The implications of using neonatal blood culture alone to estimate early onset GBS disease have both collective and individual maternal relevance. Collectively, strategies for prevention of disease in any given maternity unit will need to assess both the maternal carriage rate and the incidence of the disease in the neonate. The effectiveness of any intervention, such as intrapartum chemoprophylaxis, will rely on evidence of a reduction in neonatal disease incidence as one important outcome. A test with 29% sensitivity as found for blood culture in this study is inadequate to define either the need for intervention or the effect of intervention. Alternatively, the LPA test applied to urine is easy to implement and acceptable with a sensitivity of 88%.

For an individual mother, detection of early onset GBS disease has important implications, not only for appropriate and immediate treatment of her neonate but also for her future pregnancies. The likelihood that inadequate maternal antibody levels to GBS contribute to neonatal susceptibility to GBS disease and the reported recurrence in subsequent pregnancies suggests an increased risk for perinatal disease in future pregnancies.[16]

In conclusion, this study suggests that detection of GBS antigen in the urine by the LPA test is valuable in improving clinical neonatal practice. This is based on the evaluation of the test when applied to a clinical definition of early onset GBS disease. The sensitivity of 88% and specificity of 98% is within acceptable limits. The 99% negative predictive value is a valuable adjunct to safely limiting unnecessary antibiotic use. The increased rate of disease detection when the test was compared with traditional blood culture, has implications for appropriate antibiotic treatment of the individual neonate, as well as future siblings. This test also has a role in defining neonatal GBS disease more accurately when evaluating preventive strategies.

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Recovery of intralipid from lumbar puncture after migration of saphenous vein catheter

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Abstract

A term female infant was admitted to the intensive care unit with the diagnosis of tetralogy of Fallot with critical pulmonary stenosis. On the seventh day of life a long saphenous line was inserted that remained without complications until seven days later when the infant appeared septic. A lumbar puncture demonstrated the presence of intralipid in the cerebrospinal fluid that we interpreted as due to migration of the saphenous catheter. The child had an uneventful recovery.

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Newborns requiring long term parenteral nutrition have been managed with central venous catheters. Between 28–50% of these infants develop complications of catheterisation.[1 2] Complications are associated with low birth weight, especially less than 1000 g, lower gestational age, and a longer duration of catheter insertion as well as repeated catheterisation.[1] In this report, we describe a term baby who developed late extravasation of a long saphenous vein line into the epidural space.

Case report

An infant girl delivered at term by caesarean section weighed 3260 g and required no active resuscitation. Apgar scores were 9 and 9 at one and five minutes respectively. The child was transferred from another hospital to this centre for investigation of intermittent circumoral cyanosis. Investigations confirmed tetralogy of Fallot with critical pulmonary stenosis. She was managed with prostaglandin infusion. Balloon angioplasty was carried out on the fourth day of life through the right saphenous vein after failure to get the catheter through the umbilical vein. The procedure was complicated by difficulty in passing the catheter through the saphenous vein.

On the seventh day of life, the baby developed necrotising enterocolitis necessitating the institution of total parenteral nutrition. A long line (Dow Corning Silastic Medical) was established with ease on the eighth day of life via the left saphenous vein. Confirmation of its position in the femoral vein was carried out by withdrawing blood from the catheter and an *x* ray film (fig 1).

On the 15th day of life, seven days after insertion of the central venous catheter, she became febrile and mottled, with poor peripheral perfusion. A blood count showed neutrophilia with a leucocyte count of 51×10^9/l and young cells of 30%. A lumbar puncture revealed a milky fluid that was not under pressure and contained a triglyceride concentration of 42·6 mmol/l. No cells were found and there was no growth on culture. Fluoroscopy showed opacification of the epidural space with the tip of the catheter at lumbar level 4 and 5 (fig 2). Blood could not be withdrawn from the catheter so it was promptly removed. An electroencephalogram, ultrasound scan, and computed tomogram of the spine were normal with no evidence of masses within the epidural space. Repeat lumbar puncture one week after the incident was completely normal.

A magnetic resonance imaging scan of the spine carried out about the seventh week of life revealed only questionable narrowing of L4-L5 disc space with no evidence of cord compression or expansion and neither extradural abnormality nor aberrant vessels were identified. The child made an uneventful recovery but was readmitted with small bowel obstruction due to segmental volvulus. Postoperatively she had no complications.

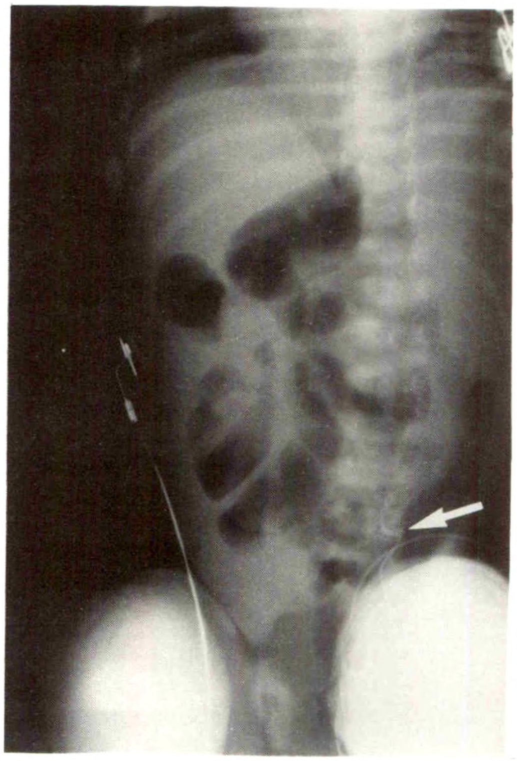

Figure 1 Radiograph contrast study immediately after surgical insertion of Silastic catheter in the left femoral vein. Note the arrow pointing to the tip of the catheter.

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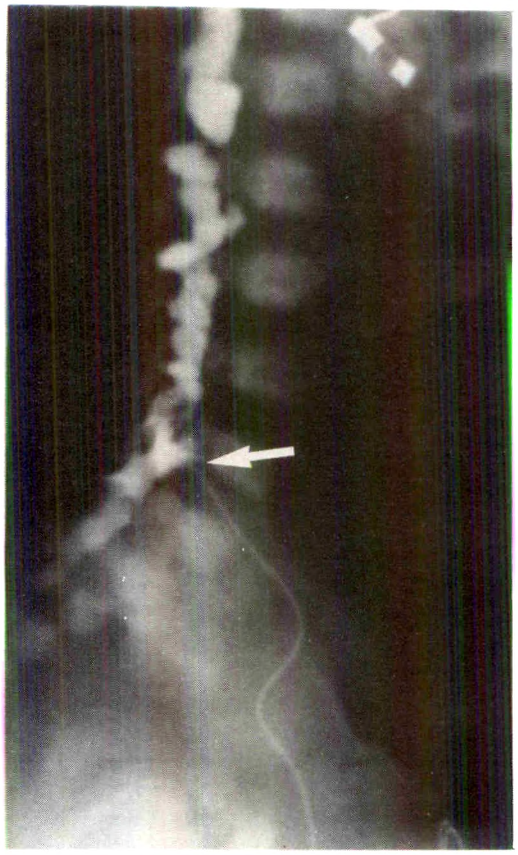

Figure 2 Lateral radiograph during fluoroscopy. Note that the contrast material outlines the epidural space and the arrow points to the catheter traversing the L4-L5 disc space.

Discussion

Complications of catheter placement are widely reported. The most common complications are thrombosis and infection. The causal organisms include *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*.[2] Other complications include catheter rupture, dislodgement, failure, leakage of fluid, and peripheral oedema.

The more serious complications relate to cardiorespiratory compromise. Respiratory difficulty may occur as a result of collections in the pleural cavity.[3] Complications are no more frequent with indwelling femoral central lines than with lines in other sites.[4] This report demonstrates that even with careful checking of the position of the catheter, displacement or migration of the catheter can still occur. A high index of suspicion is required to alert a physician to this rare type of complication. In another case reported catheterisation of the femoral vein via the left saphenous vein resulted in the infusion of the contents of parenteral nutrition into the dural and retroperitoneal spaces.[5] Whereas the clinical presentation and lumbar puncture findings were similar to ours, the position of their catheter was never established before starting the infusion, and the outcome was fatal.

We are certain that the catheter was in the right position when first placed because of the ability of the surgeon to withdraw blood from the line soon after its insertion and the radiological confirmation of its position. It must have been in place until the very end as this infant received parenteral nutrition over a seven day period through this line at a rate of 150 ml/kg/day and had a sudden deterioration with no recovery of blood from the line at that time.

One can only speculate as to the mechanisms of this rare complication. The veins of the vertebral canal form freely communicating plexuses along its length both inside and outside the canal. The internal vertebral plexuses form a continuous network between the dura mater and the walls of the vertebral canal. Because these vessels are so thin walled, it is probable that the catheter, having passed into the ascending lumbar veins, entered the intervertebral veins, ruptured its wall, thereby lodging in the epidural space (figs 3 and 4). We postulate that obstruction or thrombosis of femoral vessels may lead to increased blood flow through the paravertebral plexus, which may displace the tip of the catheter from its original position. However, we were not able to confirm this on radiological examination.

Our case report emphasises that long Silastic central catheters may become displaced at any time, even when correct placement has been documented radiologically. Furthermore, there may be no external evidence that displacement has taken place. We recommend (i) that manufacturers imprint catheters with indelible marks so that the length of tubing inside the body may be documented, (ii) that the catheters tip be radiopaque, enabling displacement to be identified on a plain *x* ray film, and (iii) that personnel caring for infants with central venous Silastic

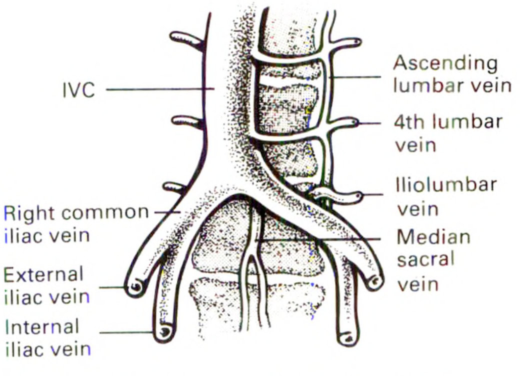

Figure 3 Inferior vena cava (IVC) and its tributaries.

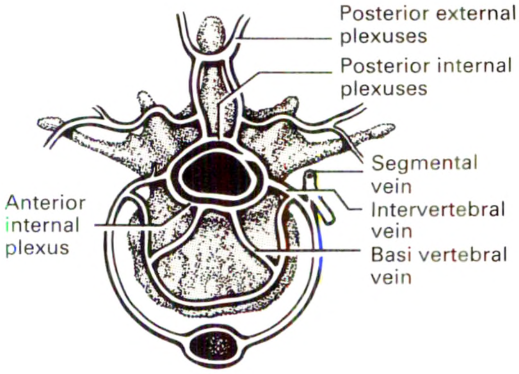

Figure 4 Venous supply of lumbar vertebrae.

catheters have a high index of suspicion of this complication, which may be asymptomatic.

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Meconium ileus in the absence of cystic fibrosis

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Abstract

Although meconium ileus in the absence of cystic fibrosis is considered a rare event, it was found that eight of 37 (21·6%) newborn infants with meconium ileus had no laboratory or clinical evidence of cystic fibrosis.

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Meconium ileus is the earliest clinical manifestation of cystic fibrosis in 10–20% of affected patients (13·4% at this clinic),[1] but it is a rare phenomenon in patients who do not have this condition. We report eight neonates with meconium ileus, who had no clinical or laboratory evidence of cystic fibrosis.

Patients, methods, and results

During the six year period, 1986–91, 37 neonates with meconium ileus were seen at the Hospital for Sick Children, Toronto. Eight (four boys) of these 37 patients (21·6%) were subsequently shown to have no laboratory evidence of cystic fibrosis, and they form the basis of this report.

The patients' characteristics are summarised in the table. Four of the eight infants were delivered prematurely (that is, less than 37 weeks' gestation), three of whom required intubation and mechanical ventilation at birth. Maternal complications included polyhydramnios (patients 4 and 7) and pre-eclampsia (patient 6), but there was no family history of cystic fibrosis. All presented with signs of intestinal obstruction with abdominal distension (with the exception of patient 5), and failure to pass meconium, and four infants developed ileal perforation. All except patient 5 required laparotomy, and three infants required bowel resection. Complications noted at surgery included ileal perforation, meconium peritonitis, meconium pseudocysts, ileal volvulus, and ileal atresia (table). Histopathology of the surgically resected specimens of small bowel revealed necrosis and haemorrhage, but lesions typical of cystic fibrosis[2] or Hirschsprung's disease were not identified. Pilocarpine iontophoresis sweat chloride tests were normal on two occasions in all patients. Genetic studies were performed on six subjects, none of whom had the ΔF_{508} deletion, which is present in 68% of patients with cystic fibrosis at this clinic.[3] Six of the eight infants had a favourable outcome and developed no gastrointestinal, nutritional, or pulmonary complications.

Patient 2, who was born at 30 weeks' gestation, required mechanical ventilation for 17 days and developed mild bronchopulmonary dysplasia. Patient 6 required continuous mechanical ventilation for 106 days for the respiratory distress syndrome, which resulted

Clinical data of the eight patients

Patient No	*Sex*	*Gestational age (weeks)*	*Age at presentation*	*Birth weight (g)*	*Clinical presentation*	*Abdominal radiograph*
1	M	36	Day 2	2730	Formula feeds for 24 hours, abdominal distension, vomiting (bilious drainage by nagogastric tube). No meconium passed after 24 hours	Distended loops with air-fluid levels, no air in colon. Barium enema: microcolon, ? distal small bowel atresia
2	M	30	Day 3	730	Ventilated for RDS (17 days): not fed, developed abdominal distension, periumbilical erythema. No meconium passed by day 2.	Dilated loops (day 1), free air in the abdomen (day 3)
3	F	40	At birth	3210	Not fed, developed abdominal distension. No meconium passed; bilious drainage by nasogastric tube	No abdominal gas; microcolon; calcification in RIF. ? Meconium cyst
4	M	35	Day 2	2630	Low Apgar scores—ventilated for 24 hours: not fed, developed ascites and raised serum transaminase values on day 2. No meconium passed by day 2	No abdominal gas. Barium enema: malrotation, proximal dilation of small bowel with free air in the abdomen
5	F	40	12 hours	3120	Breast fed, bilious vomiting. No meconium passed	Barium meal: ?mass in RIF, barium enema: patchy filling defects in colon and the last 10 cm of ileum
6	F	27	Day 2	870	Ventilated for RDS (106 days): not fed, abdominal distension. No meconium passed by day 3	Dilated bowel loops. Barium enema: microcolon
7	F	39	At birth	3500	Not fed, abdominal distension, bilious gastric aspirate	Air bubble in the stomach, no air in the rest of the bowel. Barium enema: proximal bowel dilatation microcolon
8	M	40	7 hours	3000	Breast fed, abdominal distention, bilious vomiting	Paucity of air in the abdomen, free air under diaphragm

BPD=bronchopulmonary dysplasia; RDS=respiratory distress syndrome; RIF=right iliac fossa.

in the development of bronchopulmonary dysplasia. Despite irrigation of the bowel with *N*-acetylcysteine at laparotomy, no meconium was passed, and further surgery was required at day 14 of life after a rectal perforation. Several attempts at extubation failed and this baby died at 4 months of age from lower respiratory infection, superimposed on chronic lung disease. With the exception of patients 2 and 6, all infants in our series had normal chest radiographs.

Discussion

Although all of the newborns described presented with meconium obstruction of the terminal ileum, none had clinical or laboratory evidence of cystic fibrosis. Meconium intestinal obstruction in the neonatal period can be due to three conditions (1) meconium ileus; (2) meconium plug syndrome; and (3) meconium disease (inspissated meconium syndrome).

Meconium ileus is due to mechanical obstruction of the terminal ileum with thick, viscid meconium, and in about 50% of cases is complicated by volvulus, atresia, or meconium peritonitis.[4] In cystic fibrosis, meconium ileus is thought to result from abnormal mucus production in the intestine[2] and/or impaired pancreatic enzyme or fluid secretion.[5] Meconium ileus rarely occurs in infants without cystic fibrosis,[6] but has been reported with pancreatic duct stenosis,[7] partial pancreatic aplasia,[8] ileocaecal atresia[9] as a familial condition[10 11] and a functional disorder in preterm babies.[12] The meconium plug syndrome has also been reported in cystic fibrosis.[13] In this condition, transient obstruction of the distal colon occurs, although meconium plugs in the ileum may cause complications, requiring surgery.[14] Meconium disease has been described in premature infants with very low birth weight and is not associated with cystic fibrosis.[15] In this condition meconium plugs are found in the distal ileum and proximal colon and the resulting obstruction can generally be relieved by enemas.

Although overlap between the three causes of meconium obstruction may occur, the cases we report most closely resemble meconium ileus.[4] In addition, typical complications of meconium ileus occurred in five of our cases, necessitating surgical intervention. However, sweat tests were negative in all of our patients, none had clinical or laboratory evidence of pancreatic insufficiency, and the most common deletion associated with cystic fibrosis (ΔF_{508})[3] was not present in the six infants who had genetic studies. We feel confident, therefore, that our patients did not have cystic fibrosis.

Meconium ileus in the absence of cystic fibrosis is considered a rare event and has been reported in only a few cases,[16–18] sometimes as a familial condition.[10 11] However, 21·6% of our patients with meconium ileus did not have cystic fibrosis. Although the exact cause of meconium ileus is unclear, four out of eight of the babies described were born prematurely (<37 weeks' gestation), three of whom required mechanical ventilation. It is possible that reduced intestinal motility may have contributed to the development of meconium ileus in these infants.

In summary, our report indicates that a significantly greater number of newborn infants with meconium ileus will not have cystic fibrosis than has been previously described. Definitive parental counselling should, therefore, be delayed until accurate sweat chloride tests can be obtained.

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Operative findings	*Genetic analysis*	*Treatment*	*Outcome*
Meconium ileus, meconium obstructing the ileocaecal valve. No atresia	Not done	Bowel flushed with *N*-acetylcysteine	No complications. Normal faecal fat and bentiromide study
Meconium ileus with perforation of mid-ileum	Negative for ΔF_{508}	5 cm ileal resection and end to end anastomosis	No nutritional or gastrointestinal problems. Serum trypsinogen normal. Mild BPD
Meconium peritonitis. Meconium cyst: ileal atresia with perforation	Negative for ΔF_{508}	10 cm small bowel resection, and ileostomy	No nutritional, gastrointestinal, or respiratory problems
Meconium ileus with mid-ileal volvulus and perforation	Not done	10 cm small bowel resection with end to end anastomosis and irrigation of distal bowel with *N*-acetylcysteine	Jejenostomy required for small bowel dehiscence. No nutritional or respiratory problems
No surgery	Negative for ΔF_{508}	*N*-acetylcysteine by nasogastric tube and enema	No nutritional or respiratory problems. Normal faecal fat study and serum trypsinogen
Meconium ileus, microcolon	Negative for ΔF_{508}	Bowel flushed with *N*-acetylcysteine	Severe BPD. Rectal perforation day 14. Died from respiratory failure at 4 months
Segmental ileal volvulus at mid-ileum meconium cyst, and associated ileal atresia	Negative for ΔF_{508}	Meconium cyst resection, side to end anastomosis	Normal trysinogen value
Perforated distal ileum, meconium peritonitis	Negative for ΔF_{508}	Ileostomy, no bowel resection	Raised trypsinogen value

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Validation of a portable indirect calorimetry system for measurement of energy expenditure in sick preterm infants

G J Shortland, P J Fleming, J H Walter

Abstract

A portable indirect calorimeter adapted from adult use was validated for use in preterm infants. Oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were subsequently measured in 16 preterm infants breathing spontaneously in room air (canopy mode) and in nine preterm infants receiving intermittent positive pressure ventilation (ventilator mode). Validation of the system was performed using a gas injection technique with nitrogen to simulate $\dot{V}O_2$ and carbon dioxide for $\dot{V}CO_2$. Mean errors in validation of the canopy mode were 1·4% and 0·2% for $\dot{V}O_2$ and $\dot{V}CO_2$ with limits of agreement of 0·6 (+2SD) ml/min and −1·3 (−2SD) ml/min, and 0·9 (+2SD) ml/min and −2·3 (−2SD) ml/min respectively. In validation of the ventilator mode mean errors were −1·8% and −5·05% for $\dot{V}O_2$ and $\dot{V}CO_2$ with limits of agreement of 1·02 (+2SD) ml/min and −0·74 (−2SD) ml/min, and 0·93 (+2SD) ml/min and −1·45 (−2SD) ml/min respectively.

Values of $\dot{V}O_2$ and $\dot{V}CO_2$ in 16 preterm infants in the canopy mode were 6·2 ml/kg/min (0·5 1SD) and 6·7 ml/kg/min (0·6 1SD) and in nine preterm infants in the ventilator mode 4·98 ml/kg/min (1·09 1SD) and 4·74 ml/min/kg (1·08 1SD) respectively. Mean energy expenditure was 45·5 kcal (191 kJ)kg/day for infants measured in the canopy mode and 35·5 kcal (149 kJ)/kg/day for ventilated infants. This metabolic system can be adapted for use in the newborn but accuracy is reduced when it is used in those weighing less than 1000 g.

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The measurement of the rate of oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) by indirect calorimetry may be used to calculate a number of parameters important in research into human metabolism. These include the respiratory quotient (RQ), energy expenditure, and rates of fat and carbohydrate utilisation.[1] $\dot{V}CO_2$ is also required where carbon labelled stable isotopes are infused for the measurement of substrate oxidation and estimation of whole body protein turnover.[2] The first calorimeters used a closed circuit design[3] and have progressed to open circuit indirect calorimeters[4] and ventilated hood or canopy systems.[5] Indirect calorimetry has been widely used in metabolic studies in adults and has provided much information about metabolic processes in both health[6] and disease.[7] Studies in children and infants are technically more difficult and this is particularly so for sick preterm infants. However a knowledge of energy expenditure and rates of substrate utilisation in this latter group is of vital importance in determining optimal environmental conditions and appropriate feeding regimens. There at present exists a paucity of calorimetry data on sick, and particularly ventilated, preterm infants.

Many factors have been described that may influence the measurement of energy expenditure in the infant including the effect of feeding,[8 9] medical procedures,[10] sleep state,[11] maturity,[12] and type of feed.[13] Variability in measurements from day to day have been reported[13] and investigation of infants over five days have been performed.[14] These studies have concentrated on healthy growing infants and there is a need for suitable apparatus to be used with the sick preterm infant for similar work. The difficulties that arise when using indirect calorimetry in low birthweight infants are primarily due to their very small respiratory volumes. In ventilated hood or canopy systems the change in gas concentrations for infants of between 1000 and 2500 g will be in the order of 0·05 to 0·15% when a canopy ventilation rate of about 10 l/min is used. It is important that any system used to measure $\dot{V}O_2$ and $\dot{V}CO_2$ must be able to accurately determine such small differences. Previous investigators have reported variations from expected values in $\dot{V}O_2$, $\dot{V}CO_2$ and RQ of between 2 to 5%.[15 16]

In contrast to the measurement of $\dot{V}O_2$ and $\dot{V}CO_2$ in well, stable infants, there are few reports of their measurements in the ventilated, newborn infants. Lucas *et al* have reported measurement of $\dot{V}CO_2$, but not $\dot{V}O_2$, on 11 ventilated newborn infants between 26 and 32 weeks' gestation.[17] They have suggested that by measuring $\dot{V}CO_2$ alone and taking RQ as 0·85 that errors in the calculation of energy expenditure would be no greater than 14%. In an artificial test lung recovery rates of carbon dioxide ranged from 97 to 99%. Richardson *et al* measured $\dot{V}O_2$, but not $\dot{V}CO_2$, by an oxygen replenishment technique in 14 infants with respiratory distress syndrome.[18] Combined measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ in sick infants, young children, and the newborn have been made using a metabolic monitor that employs a pneumotachometer, zirconium oxide oxygen sensor, and infrared carbon dioxide sensor.[19 20] In those systems the

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assessment of $\dot{V}\mathrm{O_2}$ is critically dependent on accurate measurement of the oxygen concentration entering the system and that the oxygen supplied is at an absolute constant concentration. Small changes in the ambient oxygen of 0·05% may lead to large errors of 30 to 100% in $\dot{V}\mathrm{O_2}$. Measurements of $\dot{V}\mathrm{CO_2}$ are less subject to error because of the low ambient concentrations of carbon dioxide. The lack of suitable validations in indirect calorimetry systems have been highlighted previously.[21] In order to undertake metabolic studies in sick low birthweight infants we have validated a portable system (Deltatrac Metabolic Monitor, Datex IC, Finland) that has been adapted for use in children by changing the flow rate through the apparatus, and tested it for its suitability for ventilated and non ventilated preterm infants. It is designed to be used as a ventilated canopy system, for those infants not requiring ventilatory support or oxygen therapy, and also in a closed circuit for ventilated infants.

Patients and methods

MONITOR

In the open canopy mode room air is drawn into a Perspex hood by a centrifugal fan at a constant flow rate of 10·3 l/min and pumped into the monitor. The Perspex hood covers the infant and a plastic skirt further covers the area of cot surrounding the infant creating a partial seal. Concentrations of carbon dioxide and oxygen are measured both in ambient room gas entering the hood, via an external sampling line, and in gas leaving the hood by an infrared carbon dioxide sensor and a paramagnetic differential oxygen sensor. With a known constant flow rate (Q), $\dot{V}\mathrm{O_2}$ and $\dot{V}\mathrm{CO_2}$ can be calculated from the difference between inspired and expired values; see equations (1) and (2):

(1) $\dot{V}\mathrm{O_2}=(Q/(1-\mathrm{FIO_2}))\times(\mathrm{FO_2}-(\mathrm{FIO_2}\times\mathrm{FCO_2}))$

(2) $\dot{V}\mathrm{CO_2}=Q\times(\mathrm{FECO_2}-\mathrm{FICO_2})$

Where $\mathrm{FIO_2}$ is the concentration of inspired oxygen, $\mathrm{FEO_2}$ the concentration of expired oxygen, $\mathrm{FICO_2}$ the concentration of inspired carbon dioxide, $\mathrm{FECO_2}$ the concentration of expired carbon dioxide, $\mathrm{FO_2}$ is $\mathrm{FIO_2}-\mathrm{FEO_2}$ and $\mathrm{FCO_2}$ is $\mathrm{FECO_2}-\mathrm{FICO_2}$. The formula for $\dot{V}\mathrm{O_2}$ includes the Haldane transformation.

In the ventilator mode gases expelled from the ventilator are collected from the expiratory port and pass to a mixing chamber via wide bore tubing and a two litre low pressure reservoir (Ohmeda anaesthetic rebreathing bag) which limits pressure and flow oscillations in the system. Carbon dioxide concentration is measured in the mixing chamber and again after dilution to the known total flow rate. Thus by measurement of carbon dioxide dilution the minute expiratory flow rate can be calculated. $\dot{V}\mathrm{CO_2}$ is calculated from the formula identical to that shown previously.

Inspired oxygen concentration is measured from a sampling line, placed in the inspiration limb of the ventilator circuit, and the difference between this concentration and the mixed gas in the mixing chamber from the expiratory limb is measured using the differential paramagnetic oxygen sensor. By use of the Haldane transformation the RQ can be calculated and $\dot{V}\mathrm{O_2}$ defined; see equations (3) and (4).

(3) $\mathrm{RQ}=(\dot{V}\mathrm{CO_2}/\dot{V}\mathrm{O_2})=\dfrac{1-\mathrm{FIO_2}}{[(\mathrm{FIO_2}-\mathrm{FEO_2})/\mathrm{FECO_2}]-\mathrm{FIO_2}}$

(4) $\dot{V}\mathrm{O_2}=\mathrm{RQ}/\dot{V}\mathrm{CO_2}$

Figures 1 and 2 summarise the operating conditions.

All values are converted to standard temperature (0°C) and pressure (760 mm Hg) dry (STPD). The metabolic monitor uses tubing that is freely permeable to water vapour and thus equalises the water vapour pressure of the gas inside with that of the ambient air. All gas samples, including dry calibration and validation gases, pass through this tubing. Thus all measurements and calibrations are under identical conditions of humidity. Further detailed information of operating conditions and formulas used for calculations can be obtained.[22]

VALIDATION

The constant flow of the system was measured by burning a 5 ml volume of 95% Analar grade ethanol ($\mathrm{CH_3CH_2OH}$) in a glass test lung (supplied by Datex, Finland) attached to the system. From a known volume of ethanol the expected oxygen consumption and carbon dioxide production are calculated; see equation (5):

(5) $\mathrm{CH_3CH_2OH+3O_2=2CO_2+3H_2O}$

As the volume occupied by a mol or g molecular weight of any gas at standard conditions is 22·414 litres (l) then it may be predicted that 1 g of ethanol consumes 3×22·414/46·069=1·46 l $\mathrm{O_2}$ (STPD) and produces 2×22·414/46·069=0·973 l $\mathrm{CO_2}$ (STPD)

This can be compared with the values measured by the apparatus and appropriate calibrations made. It was not possible with the system provided to reproduce rates of $\dot{V}\mathrm{CO_2}$ and $\dot{V}\mathrm{O_2}$ equivalent to those found in the neonate so this system was only used for calibration of the constant flow. Complete combustion of the ethanol was noted by the presence of a completely blue and even flame. Burning time for the ethanol was approximately 30 minutes.

To assess the accuracy of the measurement of $\dot{V}\mathrm{O_2}$ and $\dot{V}\mathrm{CO_2}$ in the canopy mode, at rates similar to those produced by preterm infants, nitrogen and carbon dioxide were infused at known rates into the canopy using certified calibration gas (Cryoservice Ltd, 25·2%±0·5% carbon dioxide and 74·8%±1·5% nitrogen) and a certified precision flowmeter scaled for this gas mixture (Rotameter 1100 series, KDG Instruments). Appropriate corrections

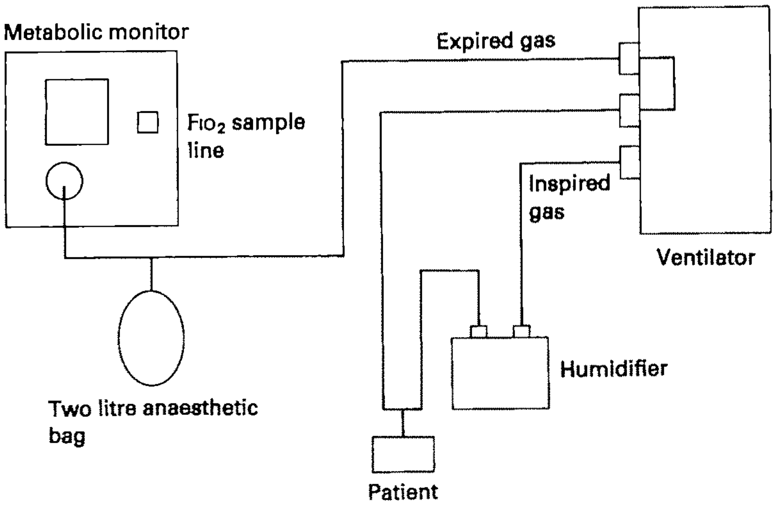

Figure 1 Operating conditions for the ventilator mode.

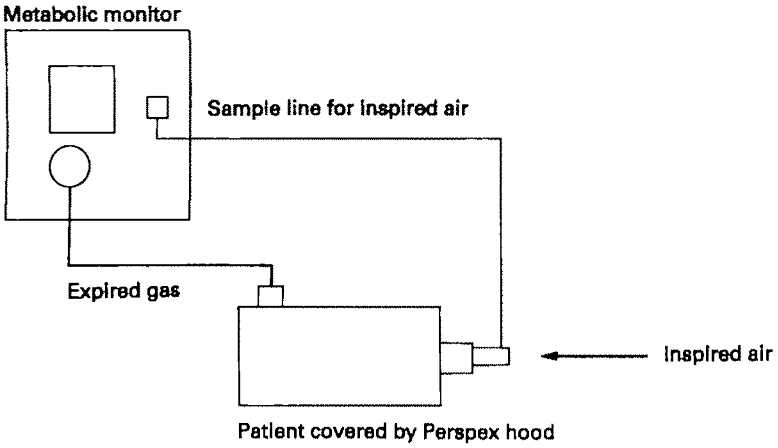

Figure 2 Operating conditions for the canopy mode

were made for operating temperature and pressure to give gas flows at standard temperature and pressure. In the ventilator mode gas was infused into the ventilator circuit via an artificial glass lung of compliance similar to that of an infant of 1500 g with respiratory distress syndrome. The ventilator was connected to gas supplies and humidifier in the normal way. With known infusion rates the injection of nitrogen and carbon dioxide will simulate $\dot{V}O_2$ and $\dot{V}CO_2$; see equations (6) and (7).

(6) $\dot{V}O_2=(F_{IO_2}/(1-F_{IO_2}))\times\dot{w}N_2$

(7) $\dot{V}CO_2=\dot{w}CO_2$ ($\dot{w}CO_2=CO_2$ injection)

Where $\dot{w}N_2$ is the nitrogen injection (ml/min) and $\dot{w}CO_2$ is the carbon dioxide injection (ml/min).

For the canopy system $\dot{V}O_2$ and $\dot{V}CO_2$ rates were simulated over a range of 5 to 24 ml/min and 4 to 30 ml/min respectively and for the ventilated system 4 to 50 ml/min and 3 to 34 ml/min respectively.

PATIENTS

Determinations of $\dot{V}O_2$ and $\dot{V}CO_2$ were made in 16 infants using the canopy mode over a period of approximately one hour. Gestational age varied between 28 to 33 completed weeks (median 31 weeks) study weight 1190 g to 2460 g (median 1822 g), and postnatal age of 7 to 19 days (median 11 days). All infants were clinically stable and in air at the time of studies and at least one hour had elapsed after their last feed.

Nine ventilated infants, gestation 27 to 36 weeks (median 28 weeks), with weights between 880 g to 2500 g (median 1300 g) were studied in the closed loop ventilator mode. All infants were being ventilated with Draegar Babylog ventilators, size 3·0 mm endotracheal tubes, and receiving intravenous glucose or parenteral nutrition with the exception of one infant receiving all nutrition by the oral route. Ages ranged from 3 to 28 days old (median 4 days). The concentration of inspired oxygen in these infants was between 21% and 60%. An assessment of the leak from the endotracheal tube was made by measurement of carbon dioxide concentrations in a plastic mask covering the face. This included a slit which allowed the endotracheal tube and nasogastric tube to pass through the mask. A partial seal was created and air was drawn from the mask at a rate of 100 ml/min as measured by an 1100 series Rotameter flowmeter. Carbon dioxide concentrations were measured by infrared analysis (Beckman LB-2 Analyser, Beckman Instruments).

All infant temperatures were within the thermoneutral range for that infant at the time of the studies. Urine was collected during the period of the study for estimation of urinary nitrogen excretion (Un) for calculation of energy expenditure values. Energy expenditure (EE) for the infants was calculated from the classical Weir equation[23]; see equation (8):

(8) EE(kcal/day)=5·67$\dot{V}O_2$ (ml/min)+1.59$\dot{V}CO_2$ (ml/min)−2·17Un (g/day)

All studies were approved by the district ethical committee and informed consent was obtained from the parents prior to the study.

Results

VALIDATION

The constant flow of gas through the analyser was calculated to be 10·3 l/min after three repeated burnings of ethanol showed less than 1% difference for the calculated value between each burning cycle. Mean error was calculated as [(measured value–true value)/true value]×100 where the true value is the test gas infusion. In addition the test gas infusion method, as the gold standard for reproducing $\dot{V}CO_2$ and $\dot{V}O_2$, was compared with values obtained from the metabolic monitor using the statistical method as proposed by Bland and Altman for limits of agreement.[24] This is able to give a 95% confidence level for individual measurements when compared with an absolute or standard and accurate method (that is test gas infusion).

Mean errors in validation of the canopy mode were 1·4% and 0·2% for $\dot{V}O_2$ and $\dot{V}CO_2$ with limits of agreement of 0.9 ml/min

(+2SD) and −2·3 mls/min (−2SD), and 0·6 ml/min (+2SD) and −1·3 mls/min (−2SD) respectively. In validation of the ventilator mode mean errors were −1·8% and −5·05% for $\dot{V}O_2$ and $\dot{V}CO_2$ with limits of agreement of 1·02 ml/min (+2SD) and −0·74 ml/min (−2SD), and 0·93 ml/min (+2SD) and −1·45 ml/min (−2SD) respectively.

Mean values for infants measured in the canopy mode for $\dot{V}O_2$ and $\dot{V}CO_2$ were 6·2 ml/kg/min (0·5 1SD) and 6·7 ml/kg/min (0·6 1SD), RQ was 1.07 and mean energy expenditure was 45·5 kcal (191 kJ)/kg/day.

Mean values for infants measured in the ventilator mode for $\dot{V}O_2$ and $\dot{V}CO_2$ were 4·98 ml/kg/min (1·09 1SD) and 4·74 ml/kg/min (1·08 1SD), RQ was 0·95 and mean energy expenditure was 35·5 kcal (149 kJ)/kg/day. We were not able to detect a leak of greater than 0·1 ml/min carbon dioxide from around the endotracheal tube in the three infants in whom measurements of leakage were made.

Discussion

There is a need for further understanding of energy requirements and substrate utilisation of different fuels in the preterm infant and newborn. Indirect calorimetry provides a means for studying this area. A system that is compact and mobile, providing the facility to measure both $\dot{V}O_2$ and $\dot{V}CO_2$ simultaneously is of great potential value in making indirect calorimetry measurements. However, rigorous validation of systems for the measurement of $\dot{V}O_2$ and $\dot{V}CO_2$ are needed as errors may be significant.

The system we have used is acceptable to the infants and their parents, is non-obtrusive in the canopy mode, and may be used in the laboratory or clinical setting. Used in the ventilator mode it may be integrated into the clinical environment without any disruption to normal ventilator function.

Validation of a system by gas injection allows measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ at levels that are found in the preterm and newborn infant in conditions identical to those of normal clinical use. We did not have facility for measurement of the gas infusion separately by mass spectometric methods.

Mean errors were small for both the canopy mode and ventilation mode. These errors would result in a maximum error of RQ measurement in the canopy mode of 1% and ventilator mode of 3·3%. These errors are well within the previous published limits and make only a small difference to RQ estimation.

The limits of agreement for the canopy mode and the ventilator mode are of a similar order. The apparent errors when using the mean error for validation are small. By using the method of Bland and Altman[24] it is possible to judge better the performance of the measuring apparatus over the whole range of values likely to be obtained in studies on newborn infants. This is preferable to using mean errors or correlation coefficients which may hide large errors in individual measurements. Our validation results show that in the small infant, particularly if less than 1000 g, there exists the possibility of significant errors in measurement, For such infants in the ventilator mode the 95% confidence limits for $\dot{V}O_2$ and $\dot{V}CO_2$ may be as high as 20% and 29% respectively if $\dot{V}O_2$ and $\dot{V}CO_2$ levels are each 5 ml/min (maximum error 1·02 ml/min and 1·45 ml/min respectively). The largest calculated error in RQ measurement for true values of 1 and 0·7 would be −0·4 and −0·3, which are unacceptably large for most purposes. At higher rates of $\dot{V}O_2$ and $\dot{V}CO_2$ these variations become less significant. We would suggest that limits of agreement be published when validating any new system. As this approach to presenting results has not previously been extensively used then there exists no previous data for comparison with other systems.

Measurements are difficult to make in situations of raised oxygen concentration in the ventilator mode where fluctuations may occur in inspired oxygen levels. This problem is reduced by sampling the inspired oxygen concentration after the humidifier which acts as a mixing chamber and reduces fluctuations. In addition it is important to note that the system as described for our methods used the Draeger Babylog ventilator and capture of expiratory gas from the expiratory outlet of the ventilator. In the other ventilator commonly used on our unit and other neonatal units (Sechrist infant ventilator IV-100B, EME) there is mixing, at the expiratory outlet, of gas from the infant with gas from a purging system that is a different concentration to that received by the infant. This results in considerable errors due to dilation of the expired gas. We have tried to eliminate this problem by use of an oxygen-air mixer between the external oxygen and air supplies and the ventilator blender, so that the purging gas and inspired gas are at the same concentration. However large systematic variations in $\dot{V}O_2$ and $\dot{V}CO_2$ and undermeasurement of these values still occur in infants measured this way. Higher flow rates at the expiratory port with this ventilator exceeding 10·3 l/min and loss of expired gas from the collecting system would explain this error. Before using this system with any other ventilators other than the Draegar Babylog it will be necessary for investigators to validate their measurements.

Values for $\dot{V}O_2$ and $\dot{V}CO_2$ in the infants in our study are similar to those previously published for infants measured in open hood[4] systems and for those on ventilators.[17 18] Energy expenditure values are also comparable with other published figures.[25 26] The mean RQ for those infants in the canopy mode was 1·07. Other studies have reported RQ values >1 in the neonate and this suggests that lipogenesis from glucose is occurring.[27] Our values were obtained over a period of 60 minutes and postprandial by at least one hour. Had we continued studies longer then net lipid synthesis from glucose may not be apparent. This equipment would be appropriate for such studies. Because the canopy mode operates in conditions of ambient air it is not recommended for use in infants receiving supplemental oxygen via a headbox in the present configuration. This does preclude using this mode to study infants with mild to moderate bronchopulmonary dysplasia who are not on ventilators but require supplemental oxygen.

Limitations with the ventilator mode include the possible loss of expired gas from around the endotracheal tube. All our infants were ventilated with 3·0 mm endotracheal tubes and leaks when measured were small. Lucas *et al* have reported similar negligible leaks.[17] If the size of leak is to be assessed with each measurement then further equipment would be required to do this with the system evaluated here. Another potential source of error is the uptake of oxygen and loss of carbon dioxide through the skin. Cartlidge and Rutter have suggested that this may account for 7% of oxygen consumption and 12% of carbon dioxide excretion for infants less than 30 weeks' gestation nursed in air during the first few days of life.[28] For measurements with the canopy mode the problem of skin losses does not occur as the infant is fully encapsulated in the hood accounting for all oxygen uptake and carbon dioxide production.

In summary we have validated a portable metabolic system for use with the preterm infant and included in our validation a range of values which also encompass the newborn term infant. The system has proved easy to use in the clinical setting but because of the wide limits of agreement care must be taken in interpretation of values of $\dot{V}O_2$ and $\dot{V}CO_2$, and hence RQ, for infants less than 1000 g. Errors in these smallest infants are sufficiently large to preclude the use of this method alone for accurate assessment of substrate utilisation.

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Fatal perinatal nephropathy with onset in intrauterine life

R J Scott, M Rochefort

Abstract

A girl, born at 29 weeks' gestation, died of renal failure aged 16 days. Postmortem histology showed diffuse mesangial sclerosis with failure of development of the cortex. This is an unusual cause of neonatal renal failure, and it demonstrates the effect of disease arising in utero and influencing the development of the kidney.

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Renal failure in neonates is rarely due to primary renal disease. We present a case of a neonate, born at 29 weeks' gestation, in whom renal failure led to death within 16 days. The pathological findings demonstrate an effect of the disease process on the maturation of the kidney.

Case report

The mother was a 28 year old white primigravida. She was negative for syphilis antibodies and had no history of renal or autoimmune disease or of hypertension before pregnancy. The parents were unrelated; the father had sarcoidosis. Serum α-fetoprotein at week 18 was raised at 3·2 × median for the gestation. Fetal ultrasound was normal.

Severe hypertension developed during the last four days before delivery, and an emergency caesarean section was performed at 29 weeks after an antepartum haemorrhage.

The infant girl weighed 1160 g and required resuscitation at birth. Her Apgar scores were 2 at 1 minute and 4 at 5 minutes; she was also ventilated.

Respiratory distress was present for the first three days and was complicated by a pneumothorax. She was treated with pancuronium, surfactant, piperacillin, and gentamicin. Her blood pressure was well maintained. Although the infant was mildly oedematous with an albumin concentration of 27 g/l, she passed urine at 5 ml/kg/hour for the first 72 hours. Urinalysis was negative and the specific gravity was below 1012. An umbilical catheter was removed at 24 hours because of left leg mottling.

At 96 hours proteinuria and haematuria were detected, but proteinuria was transient and not quantified. Her urea concentration rose to 9 mmol/l from 4·8 mmol/l at birth; creatinine was static from birth at 109 mmol/l until day 7 when it increased progressively. At that time the infant became oliguric and hypertensive and gained weight rapidly. Cardiac and renal ultrasound were normal. The baby rapidly became anuric, and peritoneal dialysis was commenced. The baby died at 16 days of respiratory failure.

Chromosome analysis was not performed and specific genetic counselling was not undertaken. A normal female sibling was born in January 1992.

POSTMORTEM EXAMINATION

A limited examination was carried out and the infant was found to be normally formed, weight 1240 g, on the 10th centile; she had normal genitalia. Internal examination showed peritoneal oedema, bile stained ascites, a congested liver, small adrenals, and two small gastric ulcers. The kidneys were enlarged, pale, and oedematous and their combined weight was 21·3 g (normal combined weight=12·9 (±33·9) g) for a 1250 g fetus.[1] There were no cysts. The ureters, bladder, and urethra were normal. The bladder was empty.

The placenta (weight 215 g) was not oedematous and showed no evidence of abruption.

MICROSCOPY OF KIDNEY (FIG 1 AND 2A)

Despite the large size of the kidneys there were only 4–5 layers of glomeruli. The nephrogenic blastema was disordered and reduced in thickness. The superficial glomeruli were small and immature, with prominent primitive epithelial cells. The deepest glomeruli had developed appropriately, but they were enlarged and showed mesangial sclerosis. There was no increase in cellularity and no crescent formation. The tubules were dilated by a mass of amorphous material that stained positive with periodic acid Schiff; they were not dysplastic and there was no evidence of acute tubular necrosis. This tubular dilation appears to be the cause of the increased renal weight.

Immunostaining showed peripheral IgM and C3 involving all the glomeruli, including immature glomeruli that could barely have acquired function.

ELECTRON MICROSCOPY (FIG 2B)

In the larger glomeruli the epithelial cells were separated from the basement membrane, with some floating free in Bowman's space. Beneath these cells was a mass of amorphous material, which was not electron dense, and therefore did not represent an immune complex deposit. The basement membrane was tortuous, with

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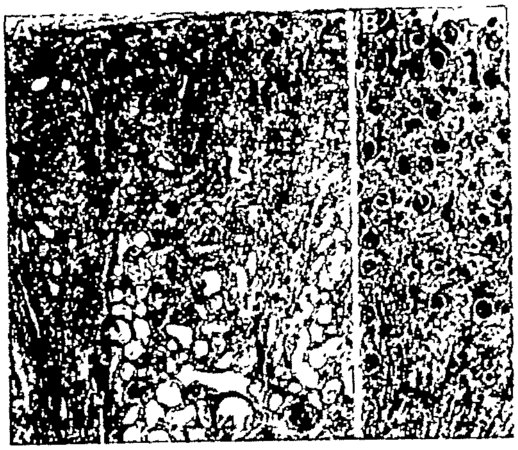

Figure 1 (A) The kidney from the case showing paucity of glomeruli and dilated tubules. (B) Normal kidney at 29 weeks' gestation (both stained with haematoxylin and eosin×30)

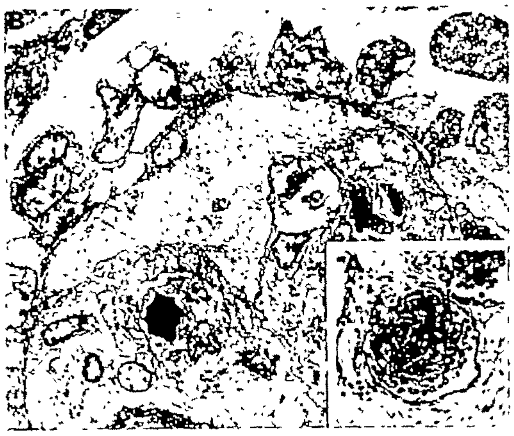

Figure 2 (A) Mesangial sclerosis in a glomerulus from the deep cortex (periodic acid Schiff×150) (B) Electron micrograph showing mesangial sclerosis, amorphous material in the subepithelial space, and detached epithelial cells (uranyl acetate lead citrate×1800)

deposition of filamentous material between the endothelium and the basement membrane proper, and there was collapse of capillary loops and sclerosis of the mesangium. In the smaller, more immature glomeruli there was a mass of amorphous material lodged between the epithelium and the basement membrane. The lamina densa was well developed.

Discussion

The interest of this case lies both in the unusual clinical presentation and the pathological findings. In our opinion the histological appearance indicates that the renal failure in this case was a disease process commencing in utero. At 29 weeks' gestation there are normally 9–10 layers of mature glomeruli and the nephrogenic blastema is prominent (fig 1B).[2] In our case (fig 1A) there were 4-5 layers of glomeruli, many of which were immature, which corresponds to the stage of development at about 20–22 weeks, and the blastema was thin and disordered. The appearance on electron microscopy (fig 2B) indicates that those glomeruli that were capable of function were suffering from hyperfiltration injury, with trapping of large molecules (including the IgM and C3 seen on immunostaining) in a leaking glomerulus.[3] It appears that a pathological process, probably a specific glomerular disease, had curtailed the formation of new glomeruli during the last seven weeks in utero.

Although there are many possible causes of renal failure in preterm neonates, in this case the insidious onset and relentless progression are unusual features. Possible acquired causes in a preterm infant are antenatal hypoxia due to pre-eclampsia or abruptio placentae, intrapartum asphyxia, polycythaemia, emboli from a catheter, or gentamicin or pancuronium toxicity. However these would all cause a more acute onset of renal failure. More importantly, no disease acquired during or after birth could have had this profound effect on development.

Many congenital causes of renal insufficiency can be excluded on morphological grounds. These include malformations of the lower urinary tract, Finnish type congenital nephrotic syndrome, polycystic disease, and renal dysplasia. The lesion in the glomeruli bears some resemblance to that seen in congenital syphilis[4] but this can be excluded on maternal serology and by the absence of immune deposits.

The renal lesion most closely fits into the category of idiopathic diffuse mesangial sclerosis (DMS).[5] This is a poorly characterised condition, probably of heterogenous aetiology, and can be familial. It is rare in infancy[4 6] and is associated with a less rapidly fatal course than in our case. It has not been described in appreciably preterm infants. However the glomeruloscerotic lesions are similar to ours, and the infants with DMS who present early and survive for a few months do show an excess of immature glomeruli.[4 6 7] In one 15 month infant there was also perpheral IgM and C3 staining in the glomeruli, without electron dense deposits on electron microscopy.[8] The precise pathogenetic mechanism remains obscure, in our case as in other cases of DMS.

We believe that this is an example of the influence on development of disease acquired during fetal life. From a practical point of view it emphasises the importance of reaching a pathological diagnosis in cases of neonatal renal failure.

We gratefully acknowledge the opinions given on the case by Professor R A Risdon of the Hospital for Sick Children, Great Ormond Street, London, and by Dr J Bernstein of the William Beaumont Hospital, Royal Oak, Michigan, USA.

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When will my baby go home?

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Abstract

The length of stay of preterm babies discharged from a neonatal nursery was determined and the predictive value of perinatal factors on the duration of stay was assessed on 762 preterm Salford born babies admitted to Hope Hospital neonatal unit between April 1986 and November 1990. The data were analysed using multiple logistical regression and forward stepwise regression analysis. Babies were discharged at a median (quartile range) postconceptional age of 36·3 (35·3–37·6) weeks. Seventeen factors were found to be strongly predictive of discharge date. The most significant predictive factor was gestational age accounting for 40% of variability compared with respiratory difficulties (6%), low birth weight (4%), sepsis (2%), and metabolic problems (1%).

Most babies are discharged at approximately the same postconceptional age despite variations in their clinical course. Gestational age at birth is the most powerful predictive factor of time of discharge.

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When the initial shock accompanying the birth of a preterm baby has passed one of the first questions asked is 'when will my baby go home?' In an attempt to answer this question and to determine the predictive value of perinatal factors we have analysed computerised data relating to Salford born babies between April 1986 and November 1990. There is little published information to help paediatricians. Although many studies report outcome in terms of morbidity and mortality in relation to gestational age,[1–5] only rarely is the postconceptional age at discharge also described.[3 5 7] This has varied between 36–40 weeks' postconceptional age with average discharge weights of 2010–2627 g. These studies have reported the information for a discrete group of infants, for example all with birth weight less than 2000 g.[6]

Nothing is lost by discharging babies as soon as they are feeding well orally rather than by waiting for an arbitrary weight to be reached,[8–10] and this has been local policy for the past 10 years. Hope Hospital provides a service to Salford, a socially disadvantaged district of the Greater Manchester conurbation with 44% of births to unmarried or unsupported women (England and Wales, 28%, 1990) and 8% low birthweight infants (England and Wales 6·7% 1990).[1]

Methods

A computerised database of all babies requiring intensive or special care admitted to Hope Hospital from April 1986 has been kept. All data of inborn preterm survivors were stored prospectively on a Tandon IBM compatible computer. The records were checked for accuracy by two doctors and a medical secretary before manual data entry.

Gestational age was assessed by a combination of mother's dates, an ultrasound scan performed before 18 weeks' gestation, clinical assessment of the baby by the formula of Dubowitz *et al*,[12] and when appropriate by examination of the anterior vascular lens capsule.[13] Gestation was thus entered to the nearest week. Records were abstracted from the database using the SCIMS operating system (Special Care Information Management System, Time Computers Ltd, Blackburn) and were analysed using the Statistical Package for Social Sciences.[14] A multiple logistical regression model was used to assess the relative importance of maternal, pregnancy, birth, and infant factors on the

Table 1 Details of infants studied

	Median	*Lower quartile*	*Upper quartile*
Gestational age at birth (weeks)	34	33	36
Birth weight (g)	2146	1714	2460
Discharge weight (g)	2261	2020	2544
Total days stay	15	5	24
Postconceptional age at discharge (weeks)	36·3	35 3	37·6

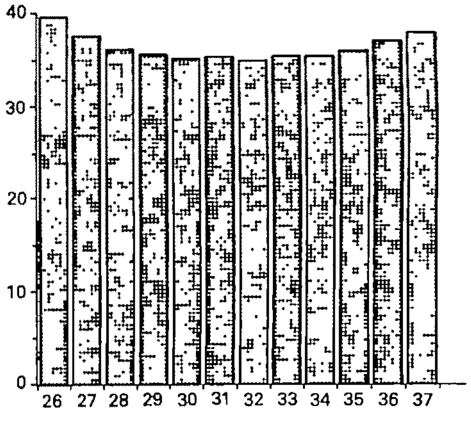

Figure 1 Postconceptional age at discharge and gestational age at birth.

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Table 2 Postconceptional age at discharge and gestational age at birth

Gestational age at birth (weeks)	*Postconceptional age at discharge (weeks)*	*Geometric mean length of stay (days*)*	*95% Confidence intervals**
24	41·6	123	
25	40·6	109	
26	39·6	95	77 to 117
27	37·5	74	58 to 94
28	36·1	57	49 to 65
29	35·5	45	39 to 53
30	35·1	36	30 to 42
31	35·2	29	23 to 37
32	34·9	20	17 to 24
33	35·3	16	14 to 19
34	35·2	9	7 to 10
35	35·9	7	5 to 8
36	36·9	6	5 to 8
37	37·7	5	4 to 6

*To nearest whole day

duration of stay. The variables were analysed in a stepwise manner to determine the independent effects of each. The study was confined to those babies discharged home from Hope Hospital; antenatal and postnatal transfers were excluded.

Results

There were 762 preterm survivors discharged during the study period. Forty five per cent were girls. Median birth weight (quartile range) was 2146 (1714–2460) g. Median discharge weight was 2261 (2020–2544) g. Median gestational age at birth was 34 (33–36) weeks and postconceptional age at discharge 36·3 (35·3–37·6) weeks (table 1). Figure 1 shows mean duration of stay expressed in terms of postconceptional age at discharge for a given gestational age at birth (see also table 2). Median duration of stay was 15 (5–24) days. For babies weighing less than 1500 g the median stay was 44 (28–66) days and for babies of birth weight less than 1000 g, 86 (65–102) days (table 3).

Table 3 Median duration of stay and birth weight

Birth weight (g)	*No of babies*	*Median stay (days)*	*Quartile range*
<1500	145	44	28–66
<1000	30	86	65–102
1001–1250	50	49	37–63
1251–1500	65	30	22–43

Table 4 Analysis of individual factors in relation to duration of stay

	R^2 (%)	*p Value*
Mother's details	2·5	0·03
Age	0·0	0·88
Height	0·0	0·86
Ethnic group	0·0	0·74
Previous neonatal deaths*	0·6	0·03
Previous stillbirth	0·1	0·33
Previous abortion*	0·8	0·02
Hypertension	0·0	0·94
Diabetes*	0·8	0·02
Parity	1·0	0·06
Presentation*	1·0	0·02
No of fetuses	0·0	0·64
Birth*	29·9	<0·001
Birth order	0·0	0·86
Mode of delivery*	4·2	<0·001
Trauma*	1·2	0·002
Asphyxia*	4·2	<0·001
Apgar score at 1, 5, 10 min*	3·4	<0·001
Suction given	0·1	0·52
Facial oxygen given	0·0	0·49
Bag and mask*	0·8	0·01
Naloxone given	0·3	0·14
Tracheal intubation*	15·9	<0·001
Labour (spontaneous/induced)	0·8	0·12
Baby	48·8	<0·001
Birth weight (log)*	35·3	<0·001
Gestational age*	39·7	<0·001
Sex	0·1	0·32
Bruising*	1·1	0·004
Fractures	0·0	0·62
Neurological problems*	10·3	<0·001
Infections*	15·1	<0·001
Metabolic problems*	9·1	<0·001
Respiratory problems*	18·7	<0·001
All	56·6	<0·001

*p<0·05

R^2 is the percentage of the variability in duration of stay explained by a particular factor

Seventeen factors were strongly predictive of duration of stay. These are shown in table 4. The categories of problems were defined as follows. Respiratory: the need for additional oxygen or artificial ventilation; neurological: the presence of fits, periventricular haemorrhage, periventricular leucomalacia, or structural central nervous system lesions; metabolic: hypernatraemia (sodium >150 mmol/l), hyponatraemia (sodium <130 mmol/l), hyperkalaemia (potassium >7·0 mmol/l), hypoglycaemia (glucose <2·5 mmol/l), or severe acidosis (pH <7·1).

Forward stepwise regression analysis of these factors against duration of stay identified five which remained strongly predictive of discharge time. This type of analysis takes into account the interrelated nature of these perinatal events and prioritises the independent contribution of each to duration of stay. Gestational age was the most significant factor accounting for 40% of the variability and was related logarithmically to duration of stay (table 5 and fig 2).

There were 47 sets of twins in the study group, 41 of whom were discharged together. In six sets there was a delay before discharge of the second twin of seven to 19 days. Of the 41 sets discharged together there was a significant disparity of clinical course in 10. The median difference in days of intensive care was 6·5 days (p<0·02 Wilcoxon signed rank sum test) for this group compared with 3·5 days for the six sets of twins discharged separately (p not significant for difference between groups).

Discussion

Most babies were discharged at approximately the same postconceptional age (36–37 weeks),

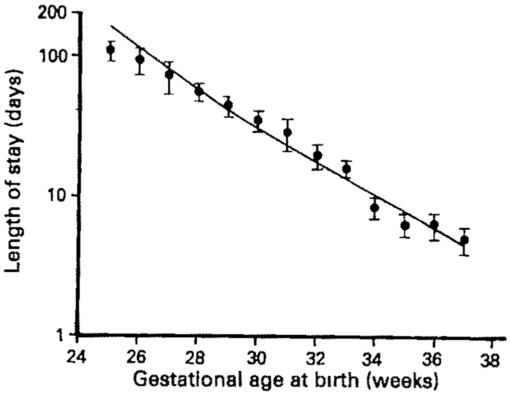

Figure 2 Predicted length of stay and gestational age at birth with geometric mean and 95% confidence intervals.

Table 5 Analysis of factors that were strongly predictive of discharge date by forward stepwise regression

Rank	Factor	*% Variability of discharge date accounted for*	*% Cumulative variability*	*p Value*
1	Gestational age	39·7	39·7	<0·0001
2	Respiratory problems	6·5	46·2	<0·0001
3	Birth weight (log)	4·4	50·6	<0·0001
4	Infections	1·8	52·4	<0·0001
5	Metabolic problems	0·8	53·2	<0·0005
	All other factors	<1·0	56·6	>0·01

which is perhaps surprising in view of the variation of clinical course. We confirmed that babies of less than 29 weeks' gestation tended to be discharged later.[7]

The observed median discharge age in this study is earlier than that reported by Lequien *et al* (39 weeks)[6] and Yu *et al* (40 weeks gestational age equivalent)[3] but comparable with Brooten *et al* (36 weeks).[10] The apparent discrepancies are not great, however, when the populations of babies are compared. In the studies of Lequien *et al* and Yu *et al* the babies were born weighing less than 2000 g[6] or below 27 weeks' gestation.[3] However there was a significant difference between the observed duration of stay and that reported by Monset-Couchard *et al* in whose study the median stay was 69 days compared with 44 for very low birthweight babies and 109 days compared with 86 in Salford babies of less than 1000 g birth weight.[7] This is unlikely to be due to differences in the proportions of light for dates babies. A higher median discharge weight of 2627 g (compared with 2261 g in Salford) was also reported in keeping with the longer duration of stay. The study of Ryan *et al* reporting an average stay of 48 days for babies weighing less than 1000 g includes deaths and is not comparable.[15]

The lower postconceptional age at discharge seen in Salford babies probably reflects the functional rather than structural discharge policy,[8] which depends upon continuing home supervision by community special care midwives.[16]

The most powerful single predictive factor of length of stay was the gestational age. The logarithmic relationship with total days of stay implies that the problems encountered by the more premature baby do not increase in a linear way with earlier gestation at delivery. It appears to be exponentially more difficult to look after such a baby for every arithmetic decrease in gestation. However gestational age also subsumes most of the confounding delaying factors, namely the presence of neurological problems, the need for prolonged ventilation, or extremely low birth weight. Although these factors did have an independent influence on duration of stay in that light for dates babies with respiratory difficulties and septicaemia were discharged a little later than those without these problems, the additional contribution to the variation in discharge date is small.

This fact is underlined by the twins in the study. Although there may be a bias to discharge twins on the same day for ease of parental visiting, only six out of 47 sets were discharged separately. These six showed a smaller variation in clinical course than the majority in whom differences of up to 19 days intensive care were noted.

Despite analysis of 31 perinatal factors, 43% of the variability in discharge date remains unexplained. It is likely that some of this variability will be related to a combination of genetic and socioeconomic factors. It was not possible to analyse these factors directly but examination of related variables namely age, parity, and a history of previous perinatal death demonstrated a contribution to duration of stay of less than 1%.

A preterm baby of more than 28 weeks' gestation is likely to be discharged at approximately 36–37 weeks' postconceptional age irrespective of perinatal history. The postconceptional age at discharge of more preterm babies approaches term. Gestational age is the strongest predictor of discharge date.

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Intermittent ductal patency in healthy newborn infants: demonstration by colour Doppler flow mapping

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Abstract

Colour Doppler flow mapping was used to determine the time of closure of the arterial duct in 51 healthy newborn infants. Initial time of closure corresponded with previous reports: 20% on the first day, 82% by the second day, 96% by the third day, and 100% by the fourth day. Twenty infants were delivered by caesarean section and followed up for seven days even if the duct had apparently closed; in six intermittent patency was demonstrated with flow in the third, fourth or fifth day, although earlier functional closure had been observed. All were found to be closed on the sixth and seventh days. It is necessary to be aware of the phenomenon of intermittent closure in any study determining or assessing the effect of any intervention on ductal patency.

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Doppler echocardiography has demonstrated that in healthy term newborn infants functional closure of the arterial duct occurs later[1–4] than previously had been reported.[5] Colour Doppler flow mapping provides a sensitive and accurate tool to detect flow through a very small arterial duct[6] which might be missed by spectral Doppler echocardiography if an arduous and careful search is not carried out.[7] We undertook a colour Doppler study of the timing of ductal closure in 1987 but did not report it as Reller *et al* did so before us.[2] However, with colour Doppler techniques we observed intermittent ductal patency in the first week of life which has not been taken into account in other reports.[1–4] As reported information on closure is becoming accepted as definitive, we considered it appropriate to report findings on ductal reopening. This should amplify and clarify the data on timing of ductal closure and ensure that misconceptions do not arise.

Subjects and methods

Fifty one newborn infants, born at term with a birth weight appropriate for gestational age, were studied. Thirty one were delivered by spontaneous vaginal delivery and 20 by lower segment caesarean section. There was no statistical difference in gestational age, sex, and birth weight between the two groups. All had normal Apgar scores at birth, and no clinical signs of cardiovascular abnormality or evidence of respiratory distress. Maternal consent was sought before the infant's inclusion in the study protocol. Newborn infants delivered by caesarean section stayed for at least seven days in the postnatal ward.

A Vingmed 700 system with a 5 MHz transducer was used for the ultrasound studies. Standard high parasternal short axis and suprasternal views were obtained to attempt to image the arterial duct and to assess its patency with colour Doppler mapping.

All infants were studied within the first 24 hours of birth and subsequently at approximately 24 hourly intervals. The 31 delivered by vaginal delivery were studied only until ductal closure occurred. The 20 delivered by caesarean section remained in hospital longer and it was possible to study them daily for the first seven days of life.

Results

Studies were made each day and the cumulative total number of infants in whom initial ductal closure had occurred was observed as follows: first day (5–23 hours) in 20% (10 of 51); second day (27–47 hours) in 82% (42 of 51); third day (51–71 hours) in 96% (49 to 51); fourth day (75–91 hours) in 100% (all 51). The mode of delivery had no apparent effect on the timing of initial ductal closure (χ^2=2·06; 0·5>p>0·1).

Six of the 20 infants studied for seven days showed intermittent patency of the duct with flow again being demonstrated on the third, fourth, or fifth day, although initial functional closure had occurred (table). Colour Doppler maps showed that all the infants had closed ducts on the sixth day and they remained closed when observed for a further 24 hours.

Two small muscular trabecular ventricular septal defects were detected by Doppler scan. These infants did not have a murmur during their hospital stay (three and seven days). The

Intermittent patency of ductus arteriosus in healthy term newborn infants

Patient No	*Days of age*						
	1	*2*	*3*	*4*	*5*	*6*	*7*
1	+	–	+	–	–	–	–
2	–	–	+	–	–	–	–
3	+	–	–	–	+	–	–
4	+	–	+	+	–	–	–
5	+	–	–	+	+	–	–
6	+	+	–	+	–	–	–

+Ductal patency demonstrated by colour Doppler flow mapping, –no ductal patency demonstrated by colour Doppler flow mapping.

infant discharged at three days developed one which is still present at 4 years of age while the other has never had a murmur although flow can still be demonstrated at 4 years of age.

Discussion

Sherman and Sahn noted that without colour flow mapping the Doppler detection of a small ductal jet can require an arduous search.[7] Colour Doppler mapping simplifies the demonstration of ductal flow and is such a sensitive technique that in older patients we have found that Doppler demonstrates even a tiny arterial duct which cannot be recognised clinically.[6] The observation of a ventricular septal defect which was inaudible in a child followed up to the age of 4 years adds further credence to the concept of minor cardiac defects which cannot be recognised by clinical examination.[6] This may indicate that the incidence of congenital heart defects is higher than previously reported.

Our findings of timing of initial functional ductal closure are similar to previous reports using spectral or colour Doppler scans.[1–4] Initial functional ductal closure occurred in the majority of patients by the second day of life and in all by the fourth. However, in previous reports observations were discontinued after initial ductal closure was noted. Our study has demonstrated reopening of the arterial duct in 30% of patients (6/20) in whom patency was monitored for seven days. The mode of delivery was found not to affect the initial timing of ductal closure[1] and this was confirmed in our patients. We have no reason to believe intermittent ductal patency should be confined to patients delivered by caesarean section.

The timing of normal ductal closure is of no clinical relevance in the normal infant. However, it may become important in studies assessing the effect of any intervention on ductal closure. Our observations suggests that final closure in newborn infants may occur later than previously reported. The possibility of intermittent ductal patency has not been monitored in previous reports but we consider that it is essential to take this into account in any future study which reports on the timing of ductal closure.

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Neonatal meningococcal conjunctivitis associated with meningococcal meningitis

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Abstract

Two infants are described in whom identical strains of meningococcus were isolated from both the eyes and the cerebrospinal fluid. This suggests that the eye may be a portal of entry in at least some cases of perinatally acquired neonatal meningococcal disease and has important implications for the management of perulent conjunctivitis in the newborn.

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Around 12 000 babies are born each year in the three maternity hospitals in Liverpool. Over the last five years we have encountered two babies who developed meningococcal conjunctivitis before developing meningococcal meningitis. We describe these infants here first, as a reminder to clinicians not to underestimate the potential seriousness of neonatal conjunctivitis, and second, because these cases demonstrate a possible mechanism for the development of meningococcal meningitis.

Case reports

CASE 1

This baby girl was born at term by assisted vaginal delivery to a healthy 19 year old primigravida woman after an uneventful pregnancy. The amniotic membranes were ruptured artificially 12 hours before delivery. At birth the infant was in good condition (Apgar score 9 at 1 minute) and weighed 3500 g.

On the second day the left eye became inflamed and a swab was taken for bacteriological culture before applying neomycin eyedrops. At 60 hours of age she had a generalised seizure lasting 30 seconds and signs of meningism developed. The lumbar cerebrospinal fluid was purulent with a white cell count 3040/mm^3 with numerous Gram negative diplococci. The infant was treated with cefotaxime and ampicillin for 14 days and anticonvulsant therapy for two weeks. She subsequently made an uncomplicated recovery.

The mother became unwell on the same day as her child with a fever and lower abdominal discomfort. A high vaginal swab was taken from her, and nose and throat swabs taken from the immediate family. She was first given a course of intravenous metronidazole and cefuroxime and, after identification of the organism, both parents received rifampicin.

Neisseria meningitidis group C type 2a was cultured from the infant's eye swab, blood, and cerebrospinal fluid as well as from the mother's vaginal swab and the father's throat swab.

CASE 2

This boy was born at 37 weeks' gestation to a healthy 18 year old primigravida woman after an uneventful pregnancy. The amniotic membranes were ruptured artificially eight hours before delivery. Diminished beat-to-beat variability of the fetal heart rate developed during the first stage of labour. The infant was born in poor condition weighing 2900 g and required resuscitation but not ventilation. The Apgar scores were 4 at 1 minute, 5 at 5 minutes, and 8 at 10 minutes. At 12 hours of age he had a brief generalised seizure lasting 20 seconds from which he immediately recovered and remained completely well for the next two days.

On day three he developed a purulent bilateral eye discharge from which swabs were taken and neomycin eye ointment commenced. By 72 hours of age he was handling less well with poor peripheral perfusion and increasingly abnormal jerky movements. Lumbar puncture yielded cloudy cerebrospinal fluid with a white cell count of 146/mm^3 with profuse Gram negative diplococci. The C reactive protein rose from 30 μg/l on day 3 to 145 μg/l on day 4.

The infant received a seven day course of benzylpenicillin and cefotaxime and was treated with various anticonvulsants before the seizures came under control. After the finding of Gram negative diplococci in the infant's cerebrospinal fluid a high vaginal swab was taken from the mother, who had remained well, and throat swabs were taken from the immediate family members. They were all treated with rifampicin as prophylaxis.

N meningitis group W 135 type P16 was subsequently cultured from the eye swab, blood, and cerebrospinal fluid of the infant. On this occasion the mother's vaginal and throat swabs failed to yield the organism.

Discussion

Neonatal meningococcal meningitis is rare. In 1988 Chugh *et al* reviewed 35 cases that had been reported since 1911,[1] and only three cases were found in a retrospective study of 280 cases of neonatal bacterial meningitis.[2] Two cases of neonatal meningococcal meningitis associated with maternal carriage of an identical organism in the birth canal have previously been reported.[3 4] In both cases the infant died. Case 1 therefore constitutes to our knowledge the third (and first reported surviving) case infected in these circumstances.

It is likely that asymptomatic carriage of the meningococcus in the genitourinary tract is increasing. A screening programme for gonorrhoea in New York in 1975 identified a rising incidence of *N meningitidis* isolated from the genitourinary tract.[5] Another North American study found the 1–2% of all urethral isolates of neisseria were non-gonoccoccal.[4]

There are biological similarities between *Neisseria gonorrhoeae* and *N meningitidis*. Gonococcal meningitis in neonates associated with gonococcal ophthalmia neonatorum has been described, and meningococcal conjunctivitis associated with meningitis in a 7 month old infant has been reported. A 13 day old infant who died of meningococcal septicaemia two days after developing a meningococcal conjunctivitis has also been reported, but in that case the cerebrospinal fluid was sterile.

Meningococcal conjunctivitis presented on days 2 and 3 in the two cases reported here. Within 24 hours both infants suffered a marked clinical deterioration accompanied by generalised seizures and bacteriologically confirmed meningococcal meningitis. This suggests that the eye may have been the portal of entry after intrapartum contamination with the organism.

These two cases demonstrate that the neonate is vulnerable to less pathogenic strains of *N meningitidis* which can be found in the birth canal. Swabs from purulent neonatal conjunctivitis should be immediately examined by Gram staining. If Gram negative diplococci are demonstrated, parenteral antibiotic treatment is advisable until culture identification is available.

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SPECIAL REPORT

Development of audit measures and guidelines for good practice in the management of neonatal respiratory distress syndrome

Report of a Joint Working Group of the British Association of Perinatal Medicine and the Research Unit of the Royal College of Physicians

Neonatal respiratory distress syndrome (RDS) is a condition of increasing respiratory distress, commencing at, or shortly after, birth and increasing in severity until progressive resolution occurs among the survivors, usually between the 2nd to 4th day. It is due, at least in part, to insufficiency of pulmonary surfactant and is mainly confined to preterm infants with imperfect cardiopulmonary adaptation to extrauterine life. In extremely immature infants severe under development of respiratory architecture contributes to the pathophysiology of the condition. The syndrome is manifest by respiratory distress (cyanosis, tachypnoea, grunting, and recession) and respiratory failure is diagnosed by blood gas analysis. Diagnosis is usually confirmed by an *x* ray film (ground glass appearance and air bronchograms), but these radiological features are not pathognomonic of RDS.

Aims of the working group

Audit of clinical practice requires an assessment of how personal practice measures up to certain defined standards. It is of course necessary for these standards (or audit measures) to be agreed beforehand by those conducting the audit. Agreement on appropriate audit measures may be reached locally, but for certain conditions such as neonatal RDS there are advantages in using audit measures which can be applied nationally. This is a sound basis for producing comparative data and it should also theoretically lead to uniform improvements in standards nationally.

A Joint Working Group of the Research Unit of the Royal College of Physicians and the British Association of Perinatal Medicine devised the present guidelines. Members of the working group are listed at the end of the paper. The working group met on the 22nd November 1990. Background papers were circulated before the meeting so that there was sufficient time for discussion and for development of the proposed audit measures. Statements of good practice are, wherever possible, supported by references to published trials of good design or meta-analyses. There were areas recognised where further research is required to clarify certain areas. These are listed in appendix A. Points of clinical practice suitable for audit are listed at the end of this paper (appendix B). In some instances the working group agreed that a course of action was appropriate, even if there was no published evidence to support it. These statements are followed by a (C) for consensus. The purpose of this document is to develop audit measures for the prevention and management of RDS. The audit measures recommended reflect 'good practice' based on a consensus view of the working group. It was not the aim of the working group to produce a detailed account of the 'best way' of managing or preventing RDS. There are too many areas of uncertainty and often little evidence to suggest that one approach to management is better than another.

These guidelines are recommended for good practice in all obstetric units and neonatal units offering intensive care to babies with RDS.

Clinical guidelines are published as they may help doctors by providing an analytical framework for the evaluation and treatment of some common clinical problems. They are not intended to replace a doctor's clinical judgment, and are not necessarily the only way in which a particular condition can be managed. They do, however, provide a framework within which audit and review of clinical practice can take place. The guidelines reflect the views of the individual clinicians who attended the workshops.

Guidelines for prenatal management

The vast majority of babies who develop RDS do so because they are born preterm. Preterm delivery occurs either because of the unanticipated and unplanned onset of preterm labour, or as the result of an obstetric decision to intervene, either because the mother is considered to be at risk, or more commonly, because of the belief that the risks to the fetus of remaining in utero are greater than the risks of being born too soon.

Every obstetric unit must have a clear protocol for the management of preterm labour. There have been no randomised controlled trials comparing antenatal with neonatal referral to centres that can provide intensive perinatal care, but the working group's view is

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that delivery should occur in a hospital where there are obstetricians experienced in managing the problems of preterm labour and delivery and where staff are experienced in neonatal resuscitation (C).

All obstetric units should have specific guidelines for antenatal transfers of women with pregnancies at above average risk. The assessment of the extent of the risk to the fetus of remaining in utero requires the appropriate application of antenatal investigative techniques and this may necessitate in utero transfer to tertiary referral units. On occasion, in utero transfer may be deemed to be unsafe, and therefore every district general hospital should have facilities available for the safe management of the labour, for safe delivery of the baby, and for adequate resuscitation and care of the infant until the baby can be transferred to a more appropriate centre. Each regional health authority should designate regional or subregional units which can provide expertise in the management of preterm labour, transfer of the infant, and neonatal intensive care.[1]

CERVICAL CERCLAGE

In some specific circumstances cervical cerclage has been shown to reduce the risk of very preterm delivery. Women who have had three or more second trimester miscarriages and/or preterm deliveries without obvious reason are particularly likely to benefit from cervical cerclage in a subsequent pregnancy.[2] This form of treatment has not, however, been shown to reduce the risk of RDS.[2]

ASYMPTOMATIC BACTERIURIA

Meta-analysis of the 12 well controlled clinical trials indicate that antibiotic treatment of asymptomatic bacteriuria reduces the risk of preterm delivery by about 40%.[3] There are no published data demonstrating that this also reduces the risk of RDS. Routine screening for asymptomatic bacteriuria at a stage in pregnancy (that is 18-21 weeks) where appropriate antibiotic treatment will be likely to prevent the infant from being born severely preterm may be beneficial in the prevention of RDS although this is not proved.

β-MIMETICS

An overview of 15 well controlled trials of β-mimetics in preterm labour demonstrates unequivocally that delivery can be delayed, and that this delay is reflected in a reduction in the incidence of preterm delivery and low birth weight.[4] Unfortunately, there is no evidence that this is translated into a beneficial effect in reducing the severity of neonatal respiratory problems,[4] although a moderate, and clinically important beneficial effect on the incidence of RDS cannot be ruled out. β-mimetic treatment in preterm labour seems most likely to be beneficial when time gained before delivery can allow other effective measures to be implemented. These include transfer of the mother to a centre with appropriate facilities for intensive care of the mother and baby and/or the administration of antenatal steroids (see below). The working group considers that the evidence is such that β-mimetics be considered in preterm labour to allow other effective management to be undertaken. In view of rare serious side effects such as pulmonary oedema, contraindications include women with cardiac disease, hyperthyroidism, or diabetes.

CORTICOSTEROIDS

Overviews of the results of 12 controlled trials provide clear evidence that corticosteroid administration to women at increased risk of early delivery significantly reduces the risk of RDS by about 50%.[5] The overviews clarify that the reduction in the odds of developing the syndrome is independent of gender and gestational age.[5] The greatest benefit in respect of RDS is seen when the time interval between the start of treatment and delivery is more than 24 hours and less than seven days. Nevertheless, some babies born before or after this optimal time interval still appear to derive benefit. The place, if any, for examination of amniotic fluid for an lecithin:sphingomyelin (L:S) ratio or equivalent test of surfactant production is unclear.

The working group recommends that either betamethasone or dexamethasone be given twice a day for two days by intramuscular injection to all women where the baby is likely to be delivered before 32 weeks of gestation. High risk pregnancies beyond 32 weeks of gestation may also benefit from antenatal corticosteroids. We suggest that the same criteria be used where there is prolonged rupture of the membranes, but in these cases the clinicians must be particularly vigilant for any evidence of infection in both the mother and/or fetus. If infection is strongly suspected, antibiotic treatment should be started rapidly and delivery expedited.

Contraindications to antenatal corticosteroids are maternal thyrotoxicosis, cardiomyopathy, and active maternal infection or chorioamnionitis. The effect of steroids on the fetuses of diabetic mothers is unclear, but we do not believe there is a definite contraindication in this particular case providing care is taken to correct the effect of the corticosteroid on the mother's blood glucose.

MODE OF DELIVERY

Delivery by caesarean section may be associated with a higher risk of RDS than vaginal delivery.[6] Where there is a choice in the mode of delivery, the working group believes that in the absence of more reliable data from properly controlled trials, caesarean delivery should be the exception rather than the rule, because of the known risk to the mother (C). This should apply both to the fetus presenting by the breech as well as the fetus with cephalic presentation. Where caesarean section is necessary, lower segment section may prove very traumatic to the small infant and in such circumstances ready recourse to upper uterine segment incision should be considered, and the implications of this discussed with the mother beforehand.

Guidelines for resuscitation

It is most important that any baby at risk of RDS should be born in a hospital that has the facilities and expertise to resuscitate and support the infant until transfer can be arranged to a referral centre (C). All relevant medical and midwifery staff should have a period of formal and practical training in neonatal resuscitation and this level of training should be regularly maintained. This includes instruction on endotracheal intubation for those with a regular responsibility for resuscitation as part of their normal duty. Others should be trained in the safe use of a bag and mask. With reference to RDS, it is particularly important to train staff in the resuscitation of infants of below 30 weeks' gestation. A written resuscitation protocol should be given to all relevant personnel.

Important goals for effective resuscitation include the need to avoid the infant becoming cold,[7 8] the need to give active respiratory support to an infant who is not breathing,[9 10] to oxygenate the infant adequately,[11] and to maintain an appropriate blood glucose concentration.[12 13]

ROUTINE INTUBATION

Unfortunately, there is a lack of fundamental data from physiological studies with which to formulate further guidelines for effective resuscitation of infants at risk of RDS. Although it is clear that the infant's airway should be stabilised from the first breath, further research needs to be done to establish the best method for doing this. There is no good evidence that babies (including very premature ones) who are breathing effectively at birth benefit from routine intubation and positive pressure ventilation. Intubation should be performed if the infant is cyanosed or making inadequate respiratory efforts.

If an infant requires intubation, the inspiratory pressure should be high enough to appropriately move the chest wall and these pressures may need to be as high as 30 cm H_2O or more (C). In general, the lowest pressure which will effectively move the chest should be chosen.

EARLY CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP)

The role of early CPAP by either nasal prong or face mask immediately after resuscitation of premature infants at risk of RDS remains controversial and further controlled clinical trials are required to resolve this.

Guidelines for ventilatory management

All infants at risk of RDS should be closely monitored for clinical and blood gas evidence of respiratory failure. Each unit that undertakes long term (>24 hour) care of these infants should have at least one consultant paediatrician with an up to date knowledge of the principles of mechanical ventilation and who should be responsible for providing a clear respiratory management protocol for all the staff working on that unit. Particular attention must be paid to the provision of modern neonatal ventilators (see below) and efficient humidification systems.

VENTILATION TECHNIQUES

There is no consensus view on the ventilator management of RDS and two basic methods exist which can be referred to as slow rate and fast rate. The slow rate method aims to start babies on the ventilator at rates of 30-40 breaths per minute (bpm) with peak inspiratory pressures (PIP) of 20-25 cm H_2O and initial inspiratory to expiratory (I:E) ratio of up to 1:1. If the baby shows deteriorating lung disease and changes in the ventilator settings are thought necessary, either increase of the I:E ratio (making the inspiratory time longer than the expiratory) or increasing PIP may be appropriate. High inspired oxygen concentrations are used if required and the PIP should be the lowest setting compatible with satisfactory blood gases.[14]

The fast rate method commences ventilation at about 60 bpm and may increase to 120 bpm if the baby is breathing at a faster rate than the ventilator. The expiratory time should exceed the inspiratory time to prevent inadvertent alveolar overdistension, and inspiratory times should be limited to a maximum of 0·5 sec throughout the duration of mechanical ventilation.[15] There is no evidence to suggest that the use of ventilation rates above 150 bpm or oscillatory ventilation techniques are of benefit (C).

It is essential to use appropriate modern mechanical ventilators which are designed for use in preterm infants. The role for patient triggered ventilators is as yet not clear.

THE INFANT'S RESPIRATORY ACTIVITY

'Fighting the ventilator' or breathing out of phase with the mechanical ventilator is agreed to be a risk factor for a variety of complications such as pneumothorax and intraventricular haemorrhage (C). It is probably impossible to recognise every baby with this pattern of respiratory interaction by simple techniques, but it is apparent in many babies by either close observation of the chest wall or looking for excessive beat-to-beat variability (>10%) on examination of the blood pressure trace measured directly from an indwelling arterial catheter/cannula (C). Hypovolaemia must also be considered as the cause of excessive beat-to-beat variability in the trace.

There is no proved policy for the management of this problem, but the baby's need for ventilation should be reviewed. If continued mechanical ventilation is considered necessary, then sedation may reduce the babies respiratory activity or a non-depolarising muscle blocker should be used. Alternatively the ventilator rate can be increased to 'capture' the respiratory rate of the baby to achieve synchrony between the baby's breathing and the ventilator. If a non-depolarising muscle relaxing agent is used, the ventilatory requirements of the baby may change and this must be anticipated.

BLOOD GAS MONITORING

There are two main reasons for monitoring blood gases. Firstly, as a guide to the need for, and the level of, ventilatory support and secondly to minimise the risk of retinopathy of prematurity. Unfortunately, there are no agreed guidelines as to what arterial oxygen tension (Pao_2) levels are safe in the prevention of this condition in very premature infants. It is therefore impossible to state 'normal' limits for pH or blood gas variables. The frequent monitoring of blood gases is, however, essential during the acute stages of RDS to assess the need for or effect of respiratory support. This is most reliably achieved through umbilical artery catheterisation or by indwelling peripheral arterial cannulae. Monitoring of oxygen by arterial sampling from an indwelling arterial catheter is the 'gold standard' measurement and continuous monitoring by a catheter tip oxygen sensor is optimal. Alternatively, non-invasive methods such as the use of transcutaneous oxygen or carbon dioxide tension monitors or pulse oximetry should be available to detect trends, but should only be used in conjunction with blood sampling, balancing the known hazards associated with prolonged intravascular monitoring against the probable (but ill defined) increased risks of retinopathy of prematurity in very preterm babies subjected to high preductal arterial oxygen pressures in the first weeks of life. Pulse oximetry may be a useful guide to oxygenation during neonatal transport, but appropriate levels of arterial oxygen saturation (Sao_2) have not yet been agreed. Acceptable levels for Sao_2 of 85-93% have been proposed, but errors in the technique of measurement are potentially great and oximetry cannot be used as the only form of monitoring arterial oxygen levels in the early phases of RDS.

There is agreement on the following blood gas values (C)

pH: Avoid arterial pH levels <7·2. When cellular metabolic function is likely to be compromised aim to maintain pH at 7·25 or above.

Pao_2: The recommended range is 6–10 kPa. The lower acceptable limit of Pao_2 in an infant with RDS may be lower than this provided oxygen delivery to the tissues is adequate as judged by haematocrit, peripheral perfusion, and base excess.

$Paco_2$: More important than the $Paco_2$ level is the pH and in general terms if this is maintained above 7·25 then the $Paco_2$ is probably acceptable. Unless there is a specific reason for inducing hypocarbia the lower limit of $Paco_2$ should be maintained above 5 kPA.

PHYSIOTHERAPY

There is no evidence to support the practice of routine physiotherapy and suction especially in the first 24 hours of life in an infant with RDS and these procedures may be hazardous (C).

ENDOTRACHEAL TUBES

There is no definite evidence that shouldered endotracheal tubes are associated with either greater or fewer complications than straight tubes.

Guidelines for the use of surfactant treatment

The use of surfactant treatment in RDS has been shown to reduce the risk of death from the disease. Meta-analyses of 34 randomised controlled trials of surfactant replacement comprising over 6000 babies show significant reductions in the risk of neonatal death both when the surfactant is given early (prophylactically) and when used for established RDS (rescue treatment).[16] These analyses show conclusively that surfactant treatment also reduces the risk of pneumothorax.

It is not yet clear whether prophylactic administration has any advantage over rescue treatment and this issue is currently being addressed in randomised controlled trials. Pending the results of these studies, the working group recommends that surfactant should be given as rescue treatment because this is less expensive. There is currently a major study being conducted on costing of surfactant throughout the UK and more accurate information will shortly become available.

Further research must be undertaken to establish whether synthetic or natural forms of surfactant are more effective, and their efficacy in infants below 26 weeks' gestation.[17] A further unresolved question is whether surfactant is cost effective in infants over 31 weeks' gestation particularly when given prophylactically.[18 19] The answers to these questions will be obtained by further well designed controlled studies and participation of individual units in these trials is to be encouraged.

Surfactant should be given by practitioners who are aware of the short and long term risks of the treatment (related to rapid changes in both respiratory and cardiovascular function) so that rapid changes in physiological state can be detected and acted upon in a neonatal intensive care environment.

Complications of RDS and guidelines for their prevention

The presence of RDS increases the risk of complications in other systems including brain (periventricular haemorrhage and/or leucomalacia), bowel (necrotising enterocolitis) and circulation (hypotension, patent ductus arteriosus). The working group believes that the risk of at least some of these complications may be reduced by ensuring gentle delivery, rapid and effective resuscitation, avoidance of hypothermia, hypoglycaemia, and hypoxaemia (C). Acidosis should be investigated in order to identify underlying causes which may need treatment in their own rights. Severe acidosis should be corrected. A bolus injection of sodium bicarbonate may cause rapid changes in serum osmolality and is to be avoided. Slow correction, over an hour or two, is usually preferable.

CARDIOVASCULAR STABILISATION

It is essential to monitor blood pressure so that hypotension can be promptly recognised, its cause assessed, and appropriate treatment offered. Facilities for intravascular blood pressure monitoring should be available, but non-invasive blood pressure measurement using the Doppler technique may give a reliable estimate of systolic pressure. Further studies of the normal range of blood pressure in very premature infants are needed, but at the present time the working group agrees that a mean arterial blood pressure equivalent to the gestational age in weeks is adequate as a minimum value (C).

Hypotension should be treated initially with colloid or blood if there is the possibility of hypovolaemia (C). The effectiveness of inotrope infusion in the preterm newborn has not been proved, but a starting dose of dopamine 10 μg/kg/min may be needed in the preterm neonate as they are relatively resistant to this form of treatment. Its use must be avoided in the presence of hypovolaemia.

BRAIN

Preterm cerebral injury (periventricular haemorrhage or leucomalacia) is to some extent related to perturbations of cerebral haemodynamics.[20] In particular, prevention of the infant fighting the ventilator may reduce the risk of periventricular haemorrhage,[21] but further studies are necessary to assess the effects of sedation and muscle relaxation both on the reduction in frequency of intracranial lesions and their effects on the cerebral circulation.

DELAYED CLOSURE OF THE DUCTUS ARTERIOSUS

When the infant is requiring mechanical ventilation for RDS and there is evidence of a patent ductus arteriosus with significant left to right shunt (diagnosed either clinically or with ultrasound), indomethacin should be given and preferably before congestive cardiac failure occurs.[22 23] Treatment should also be considered for non-ventilated infants requiring oxygen who show signs of a large left to right shunt diagnosed clinically or with ultrasound.

Indomethacin given intravenously may be associated with reduction in blood flow to brain,[24 25] kidneys and bowel,[26 27] but this does not appear to cause clinical problems. The optimal dosage schedule is not clear and this requires further clinical studies. The working group believes that either three doses of 0·1 mg/kg every 12 hours or 0·2 mg/kg/day for three days is effective (C). A platelet count of $<100\times10^9$/l, significant coagulation impairment, and renal dysfunction are important (but not necessarily absolute) contraindications to indomethacin treatment. If closure of a significant ductus arteriosus has not been achieved medically surgical ligation by an experienced surgeon should be considered (C).

NECROTISING ENTEROCOLITIS

There are few objective data to suggest that the risk of necrotising enterocolitis can be reduced by alterations in the management of RDS. The working group agrees that the risk of necrotising enterocolitis can be minimised by avoidance, or rapid treatment, of shock and by the practice of general measures to maintain homoeostasis (C).

Adequate nutrition is an important part of the management of RDS (C). Facilities for total parenteral nutrition must be available, but minimal enteral feeding should be considered in infants with stable or improving RDS (C). There is also no evidence that uncomplicated umbilical catheterisation increases the risk of necrotising enterocolitis.

Chronic lung disease

This has been defined as the requirement of supplementary oxygen after 28 days from birth.[28] It has been shown that an additional oxygen requirement in a prematurely born infant after 36 weeks' postmenstrual age is a better predictor of severe pulmonary outcome.[29] The majority of these infants will have bronchopulmonary dysplasia. Steroids reduce the duration of mechanical ventilation in preterm infants and should be given to those who have not improved by two weeks after birth.[30–34] This benefit outweighs any potential side effects (C). The dose and duration of steroid treatment are unclear, but it should initially be given as a short course and continued if a definite response is seen (C). Dosage reduction can then be titrated against clinical progress. The role of steroid treatment in non-ventilator dependent babies who remain in oxygen is not established. The place of either early steroid administration or vitamin A prophylaxis for this condition is unproved.

There is no evidence that other treatments for bronchopulmonary dysplasia including bronchodilator treatment and diuretics have a definite beneficial effect. Diuretics are indicated for episodes of cardiac failure associated with bronchopulmonary dysplasia (C), but their effectiveness as long term treatment is uncertain. If diuretics are used, consideration should be given to the use of a calcium sparing regimen. Antibiotics should only be used for active infection (C).

Treatment of babies with chronic lung disease requires facilities for long term monitoring of oxygenation state (C). Non-invasive oxygen saturation monitoring is probably most accurate, but at present firm recommendations for the optimal range of saturation cannot be agreed.

Appendix A: Areas for further research

The working group identified a number of areas where further controlled clinical studies or more basic research at a physiological level may considerably enhance our management of the infant with RDS. The major areas are summarised here.

(1) Does cervical cerclage in women at high risk of preterm labour reduce the overall risk of RDS in their infants?

(2) Does routine screening for asymptomatic bacteriuria at 18-21 weeks and appropriate antibiotic treatment reduce the overall risk of RDS in infants of these women?

(3) Does suppression of preterm labour with β-mimetics result in a reduction of risk of RDS?

(4) Does examination of the amniotic fluid for L:S ratio (or equivalent test of surfactant production) help in the prevention of RDS in preterm infants?

(5) Are antenatal steroids of benefit in reducing RDS and its complications in infants over 32 weeks of gestation?

(6) Is there a benefit of antenatal corticosteroids in diabetic women with preterm labour compared with the potential risks to mother and infant?

(7) What are the physiological effects of different methods of resuscitation on the immature infant and do these methods help to reduce the severity of RDS?

(8) What is the best method for the early physiological stabilisation of the airway and lungs in preterm infants at risk of RDS?

(9) What is the role of early CPAP immediately after resuscitation of preterm infants and does this reduce the risk of severity of RDS?

(10) What is the role of patient triggered ventilators in the management of preterm infants with RDS?

(11) In infants who 'fight the ventilator', does matching the ventilator rate to that of the baby effectively resolve this condition? Is this a feasible method of clinical management in preterm infants?

(12) What are safe levels of Sao$_2$ in infants with RDS?

(13) What are the effects of different methods of ventilatory support on cerebral oxygenation and haemodynamics?

(14) Are straight endotracheal tubes of benefit compared with shouldered tubes in preterm ventilated infants?

(15) Is prophylactic surfactant therapy in preterm infants at risk of RDS cost-effective?

(16) What is the most effective and safe surfactant for use in preterm infants?

(17) Is surfactant cost effective in infants over 31 weeks of gestation and below 26 weeks of gestation?

(18) What is the normal range of blood pressure measurements in preterm infants over a wide range of gestational ages?

(19) Is inotrope infusion of benefit in hypotensive infants with RDS? What is the optimal dosage regimen?

(20) What is the effect of sedation and/or muscle relaxation on the cerebral circulation?

(21) What is the optimal dosage regimen for indomethacin use in the management of patent ductus arteriosus in preterm infants with RDS?

(22) What is the optimal dosage regimen of corticosteroids in the management of infants with chronic lung disease after RDS?

(23) What is the indication for corticosteroid use in non-ventilator dependent babies who require prolonged oxygen treatment after RDS?

(24) What is the role of early corticosteroid treatment in the management of infants with RDS who are at risk of chronic lung disease?

(25) What is the role of other treatments such as vitamin A, diuretics, and bronchodilators in the prevention or management of chronic lung disease?

(26) What are the safe levels of Sao$_2$ in infants with chronic lung disease?

Appendix B: Proposed audit measures

OBSTETRIC UNITS

(1) Does the obstetric unit have a clear written protocol for the management of preterm labour?

(2) Does the obstetric unit have written guidelines for deciding on in utero transfer of at-risk pregnancies?

(3) Does the obstetric unit have a written policy for evaluating every woman in preterm labour for risk/benefit of (a) β-mimetic tocolytic treatment and (b) antenatal corticosteroids?

(4) Does the obstetric unit have a policy to discuss with the mother requiring caesarean section the implications for upper uterine segment caesarean section should this prove necessary?

(5) Is a formal and practical resuscitation training programme for the prematurely born infant in place in every labour ward? How often are staff retrained?

(6) Should a baby be born preterm and unexpectedly in a unit unable to offer long term neonatal intensive care, does the unit have appropriate facilities and staff skilled in looking after that baby until a team arrives from the hospital of referral? How many staff in any unit giving care to premature infants have received English National Board training in neonatal intensive care?

(7) Was the body temperature of a preterm infant above 36°C on arrival in the neonatal unit?

NEONATAL INTENSIVE CARE UNITS

(8) Does every neonatal unit undertaking intensive care have one consultant responsible for establishing a protocol for neonatal mechanical ventilation? Is there a written policy?

(9) Are the mechanical ventilators used for infants with RDS designed for this use? Do the staff understand the principles which govern the functioning of ventilators?

(10) Is there a written policy of acceptable

limits for blood gas and pH variables for preterm babies with RDS? Is there a written policy for acceptable SaO_2 ranges?

(11) If exogenous surfactant is being used, have the staff on the newborn intensive care unit been instructed about the rapid respiratory and cardiovascular changes induced by some of these agents? Is the unit appropriately staffed and equipped to monitor these changes and respond accordingly?

(12) Does the unit have a written policy governing the use of indwelling arterial catheters including their supervision, so that ischaemic complications can be promptly recognised and treated?

(13) Are facilities for dispensing and monitoring a total perenteral nutrition regimen available for infants with severe RDS?

(14) If an infant with RDS is ventilator dependent, with radiological evidence of chronic lung disease and dependent on additional oxygen at 2 weeks, are steroids considered?

Background papers

- Prenatal care to reduce the risk of neonatal idiopathic respiratory distress syndrome: Dr Adrian Grant.
- Resuscitation of the premature infant: Dr David Field.
- Surfactant therapy: Dr Henry Halliday.
- The complications of RDS and their prevention : Dr Janet Rennie.
- Chronic lung disease: Dr Rosamond Jones.

The background papers can be obtained from the Publications Department of the Royal College of Physicians, 11 St Andrews Place, London NW1 4LE. The cost is £5 to cover photocopying and postage.

Members of the working group Malcolm Levene (co-chairman, professor of paediatrics), Malcolm Chiswick (co-chairman, consultant paediatrician), David Field (consultant paediatrician), Stewart Forsyth (consultant paediatrician). Harold Gamsu (consultant neonatologist) Adrian Grant (Director, Perinatal Trials Service) Anne Greenough (consultant paediatrician), Henry Halliday (consultant neonatologist), Judith Hetherington (clinical nurse adviser), Edmund Hey (consultant paediatrician), Anthony Hopkins (Director, Research Unit of the Royal College of Physicians), Rosamond Jones (consultant paediatrician), David Lloyd (consultant neonatologist), Una MacFadyen (consultant paediatrician), Anthony Milner (professor of paediatrics), Janet Rennie (consultant paediatrician), Osmund Reynolds (professor of neonatal paediatrics), Michael Silverman (consultant paediatrician), Paul Vinall (consultant obstetrician), Michael Weindling (consultant paediatrician).

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CONTROVERSY

Surfactant replacement therapy—time for thought

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The era of surfactant replacement therapy is upon us—there are many such treatments and some are now becoming commercially available and we may expect claim and counterclaim among the clinical and commercial interests. Undoubtedly, such substances confer benefits to most of the recipients. The oxygenation of blood improves and in some studies a reduction in mortality has been reported.[1] As such, these achievements should be saluted; anything that clearly can be shown to benefit sick preterm infants should be widely employed.

Before this happens, however, clinicians should pause for mature reflection and study the published data in minute detail. What causes concern to some is that there may be misuse of these substances, that expectations may be too high, and that ultimately we may disillusion ourselves and conceivably may harm some of our patients.

Most trials have been multicentre as none of us have sufficient patients to provide answers in a working lifetime. Entry of patients into trials is therefore based on the clinical judgment of many separate individuals. This means that the possibility of inconsistency increases: if 20 neonatologists look at 100 breathless babies, it is unlikely that they will agree on a diagnosis in all cases. Further, it is unlikely that every baby enrolled in these trials was seen first by a consultant neonatologist as many will have been born in the middle of the night so the error may be further magnified by inexperience. In addition, management subsequent to surfactant administration varies within and between trials so it is difficult to discern clearly the whole truth.

However, this is not my major worry. It is possible that among the hundreds of babies who have received surfactant replacement therapy, there are some babies who might have been better left alone. I am really referring to the tiny, cold, asphyxiated baby who needs our help most but who is at the limit or is possibly beyond the range of our knowledge. It is possible that such babies will do badly no matter what is done after birth—they do not suffer only, or in some cases, at all from surfactant deficiency respiratory distress syndrome. In the opinion of some, these babies should be excluded from the trials but in many instances this is not the case. For example in the OSIRIS protocol of February 1990 the entry criteria do not exclude infants of extremely low birth weight or in poor condition at birth but it does state that there should be 'no contraindications judged by the clinician responsible for care'. The Curosurf trials also made no exclusion for condition at birth.[2] The Exosurf trial, coordinated by Long,[3] excluded babies of ≤750 g but made no allowance for features such as low Apgar scores or hypothermia. These exclusions were similar to those in the SURVANTA trials.[4] While one accepts the extreme difficulty experienced by designers of major trials it might have been better had rigid entry criteria been employed and those extremely small babies already referred to were excluded.

There are two outstanding worries about the long term effects of respiratory therapy in these babies: bronchopulmonary dysplasia (BPD) and intraventricular haemorrhage (IVH). Morley in his recent review states that 'surfactant treatment has a variable effect on the incidence of BPD'.[5] Long, in explaining why BPD was not reduced in a trial of a synthetic surfactant (Exosurf) reasons that this problem may be dose related or may be due to a type II error because of the relatively small sample size in that study. This may be but we must not overlook perhaps more obvious explanations. This condition is caused by barotrauma and it is likely that the longer the duration of time that a baby stays on a ventilator, the more likely he or she is to develop BPD. Tiny babies may require ventilator assistance for reasons other than respiratory distress syndrome, they are extremely small and weak and may be unable to sustain respiration. It is therefore likely that these very small babies may require prolonged ventilation and therefore be at major risk of developing BPD.

Again the effect of surfactant therapy on the incidence of IVH is inconsistent.[4–6] This is scarcely surprising for a variety of reasons notably the fact that respiratory distress syndrome is not the only cause of IVH. This condition may occur in utero and, in many cases, may be preset to occur at a later stage by the time of delivery. Such babies are likely to be the smallest.

The effect of surfactant on mortality again varies, although there would appear to be an overall reduction. Merritt *et al*, quoting Hack and Fanaroff, state that there has been no overall reduction in deaths in babies of less than 750 g at birth in approximately the past decade.[7] These babies then present a major challenge but in the study of Merritt *et al* using human surfactant, although the mortality rate overall was significantly reduced 'the 17·5% of infants with birth weights of less than 0·75 kg accounted for 67% of all deaths'. They also state that 'the use of surfactant in infants of lower weights may improve survival rates but also may be associated with a higher incidence of chronic lung disease among survivors'. This should reinforce our hesitancy.

The purists may argue that conclusions can only be drawn when all the data are available. I certainly accept the scientific logic of this attitude but I have a sneaking suspicion that by adhering to such august principles we are in danger of rediscovering the wheelbarrow.

What appears to be clear is that if surfactant therapy is given to babies of a reasonable size and in good condition at birth a good outcome should be expected. My view is that to administer this treatment to tiny, cold acidotic babies is to court disaster. For such babies we require to sit down and think again.

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Commentary

I agree with Professor McClure. The time for surfactant therapy has arrived but he is right to encourage caution and scepticism about individual clinical trials. Some of the trials have enrolled highly selected groups of babies, for example only babies weighing more than 700 g, on a ventilator, in more than 60% oxygen, or who have no complications. The results are then interpreted as applying to all babies.

However, there is now the most impressive body of data in the history of neonatology from multicentre, double blind, placebo controlled, randomised trials showing that surfactant replacement therapy saves lives and reduces morbidity. Surfactant used for prevention or treatment has been shown to be both safe and effective.

Surprisingly, Professor McClure has suggested that extremely small, hypothermic, asphyxiated babies should be excluded from the trials. I'm not quite sure he believes that they 'might have been better left alone', particularly as this is just the baby 'who needs our help most but who is at the limit or is possibly beyond the range of our knowledge'. If we do not study such babies they will remain beyond our knowledge. Their extreme immaturity might suggest that they will not respond dramatically to surfactant treatment. However, we will never know if we do not enter them into appropriate trials.

It is very difficult to obtain enough data from extremely low birthweight babies because they are relatively rare. In consequence most studies only allude to the possible effects in this group. The following information is available from published randomised controlled trials about the effect of treating extremely low birthweight babies with surfactant.

In a multicentre randomised trial placebo or Exosurf (5 ml/kg) was given to 215 babies with birth weights of 500 to 699 g.[1] Treatment with Exosurf was associated with a significant improvement in oxygen requirement, persisting for three days. The incidence of pneumothoraces was significantly reduced from 25/109 (23%) to 11/106 (10%), and deaths from respiratory distress syndrome were significantly reduced from 26/109 (24%) to 15/106 (14%). The incidence of other complications was not altered except that pulmonary haemorrhage occurred significantly more frequently in the Exosurf treated babies at 12/106 (11%) compared with 2/109 (2%) for the controls.

A randomised trial compared calf lung surfactant administered at 90 mg in 3 ml either prophylactically (n=235) or as rescue treatment (n=244) to babies less than 30 weeks' gestation, with repeated doses as necessary.[2] It was shown that there was a highly significant reduction in mortality in the babies less than 26 weeks who were treated with surfactant prophylactically 21/85 (25%) compared with rescue treatment 33/72 (46%). The incidence of pneumothorax was also reduced in the babies less than 26 weeks treated prophylactically 6/85 (7%) compared with the group given rescue treatment 13/72 (18%). There was no other significant effect. There was no indication that prophylactic therapy caused such small babies any harm.

In the ten centre trial of ALEC prophylaxis to babies between 25 and 29 weeks' gestation, the neonatal mortality for babies of 25 to 26 weeks' gestation was reduced from 15/32 (47%) to 13/43 (30%).[3] The sample size was small and this 36% reduction in mortality failed to reach statistical significance. The effect of artificial surfactant was equivalent to babies being older by over one week of gestation.

These effects of surfactant treatment on extremely immature babies although relatively preliminary, are consistent. They show that surfactant treatment for these extremely low birthweight babies has important beneficial effects. The only adverse effect so far reported is pulmonary haemorrhage with Exosurf. This has not been reported so far with other surfactants, although many trials have excluded babies less than 700 g and the number of such tiny babies in the other trials is relatively small.

Surfactant treatment has not been shown to have much effect on brain haemorrhages and chronic lung disease in extremely small babies.

Professor McClure is right to be cautious about the use of this new and expensive treatment but I am encouraged by the data available so far and believe we should be helping these vulnerable babies with one of the best and least toxic treatments available to neonatologists. The important thing to watch in the future is whether surfactant treatment has any effect on long term morbidity in this group. The overall results on follow up published so far are encouraging.

Part of the fascination of research is that one's preconceived ideas are often proved wrong when proper studies are done. I think doubts about the benefit of surfactant for extremely immature babies may be just such a situation.

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CURRENT TOPIC

Diagnosis and management of inborn errors of metabolism—an update

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Since this topic was last reviewed rapid advances have been made in our understanding of inherited metabolic disease.[1] Much of this increased knowledge has been stimulated by the application of molecular genetic techniques to the study of human disease. In addition clarification of the function of various subcellular organelles has led to the recognition of a number of new disease states.

An aggressive approach to diagnosis and treatment remains the correct therapeutic option. The widespread availability of accurate imaging equipment and the advances in electrophysiological techniques have improved our ability to provide an early, accurate prognosis for most affected infants.

Despite our increased understanding of the pathophysiology of inherited metabolic disease the long term prognosis for many disorders remains poor, especially in those infants where there is a significant delay between the onset of symptoms and diagnosis and treatment. Arteriovenous haemoperfusion is being increasingly used as the method of choice for removal of toxic intermediary compounds and peritoneal dialysis is reserved for those infants in whom vascular access is not possible.

It is essential that the basic 'metabolic screen' is supplemented by a sample of blood (collected in a 5 ml EDTA tube) for subsequent DNA analysis. This is particularly important for infants suspected of having medium chain fatty acyl CoA dehydrogenase deficiency (MCAD) where analysis for the common mutation is often the quickest method of establishing the diagnosis and will detect 90% of cases within the white population.[2]

Management of a child with an inborn error of metabolism while awaiting results is still based on attempts to rapidly induce an anabolic state. Glucose and insulin and the use of lipid emulsions remain the major therapeutic thrust during this period, supplemented by arteriovenous haemoperfusion. The 'blunderbuss' approach to treatment using a megavitamin cocktail can no longer be routinely recommended. Specific vitamin treatment *after* diagnosis of a disorder known to be vitamin responsive is appropriate.

The necropsy remains important in those infants for whom a diagnosis has not been found. In addition to blood, urine, cerebrospinal fluid, and skin fibroblasts, a muscle biopsy specimen should be collected and snap frozen. Muscle tissue is essential if a mitochondrial cytopathy is thought to be responsible for the infant's illness.

Appendix *Metabolic disorders that may present as severe neonatal illness*

● **Carbohydrate metabolism**

Galactosaemia produces cataracts and severe liver disease, the other members of this group usually present with a combination of hypoglycaemia and lactic acidosis (see also **Mitochondrial disorders**). Hereditary fructose intolerance requires a fructose load before symptoms appear

Disorders	*Enzyme deficiencies*
1 Galactosaemia ('classical')	Galactose-1-phosphate uridyl transferase
2 Glycogen storage disease	
Type Ia	Glucose-6-phosphatase
Type Ib	'Translocase'
3 Fructose	Fructose-1-6-bisphosphatase
	Aldolase (hereditary fructose intolerance)
4 Lactic acidosis	Pyruvate carboxylase
	Pyruvate dehydrogenase*
	Phosphoenolpyruvate carboxykinase

● **Amino acid disorders**

Presentation may be variable, but central nervous system dysfunction is common. In maple syrup urine disease the urine has a characteristic odour. Acute hereditary tyrosinaemia causes severe liver disease and renal tubular dysfunction

Disorders	*Enzyme deficiencies*
5 Maple syrup urine disease	Branched chain ketoacid decarboxylase
6 Non-ketotic hyperglycinaemia	Glycine cleavage system
7 Tyrosinaemia type I	Fumaryl acetoacetase

● **Organic acid defects**

Present with a combination of lethargy, seizures, ketoacidosis, neutropenia, hyperammonaemia, and hyperglycinaemia Hypoglycaemia is common Isovaleric acidaemia and glutaric aciduria type II produce an odour of 'sweaty feet'

Disorders	*Enzyme deficiencies*
8 Methylmalonic acidaemia	Methymalonyl CoA mutase (and others)
9 Propionic acidaemia	Propionyl CoA carboxylase
10 Isovaleric acidaemia	Isovaleryl CoA dehydrogenase
11 Glutaric aciduria type II	Glutaryl CoA dehydrogenase
12 MCAD deficiency	Medium chain fatty acyl CoA dehydrogenase

Appendix *continued*

● Urea cycle defects

Clinical features are due to hyperammonaemic encephalopathy. Hiccoughs are common The illness is more severe the more proximal the defect in the cycle.

Disorders	*Enzyme deficiencies*
13 Carbamyl phosphate synthetase deficiency	
14 Ornithine carbamyl transferase deficiency	
15 Citrullinaemia	Argininosuccinic acid synthetase
16 Argininosuccinic aciduria	Argininosuccinic acid lyase
17 Argininaemia	Arginase
18 Transient hyperammonaemia of prematurity	Unknown

● Peroxisomal disorders[3]

Defects of peroxisomal biogenesis and specific deficiencies of peroxisomal enzymes can be associated with profound neurological abnormalities as well as a typical dysmorphic presentation Only the more common disorders are mentioned below

Disorders	*Enzyme deficiencies*
19 Zellweger's syndrome	Peroxisomal biogenesis
20 Rhizomelic chondrodysplasia punctata	Multiple
21 Neonatal adrenoleukodystrophy	Multiple

● Mitochondrial disorders[4,5]

Mitochondrial disorders are becoming increasingly recognised as a cause of neonatal metabolic acidosis and encephalomyopathy With some disorders multisystem disease is common, but the central nervous system and skeletal muscle seem particularly vulnerable. Lactic acidosis is a useful biochemical marker, but the ultimate diagnosis depends on a combination of clinical picture, histological findings of skeletal muscle biopsy, biochemical analysis of the respiratory transport chain in muscle tissue, and an analysis of mitochondrial DNA for deletions and other mutations

● Miscellaneous

Disorders	*Enzyme deficiencies*
22 Pyridoxine dependent seizures	Unknown
23 Lysosomal storage disease†	Various

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*Is associated with severe abnormality in central nervous system differentiation in some patients, for example absence of corpus callosum and other defects

†A number of lysosomal storage disorders have been reported as presenting with hydrops fetalis

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PERSONAL PRACTICE

Initial experience of screening for retinopathy of prematurity

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The initial results of the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (ROP) in the USA,[1] published in 1988, showed a significant reduction in the number of visual complications in babies treated with retinal cryotherapy for stage 3 'threshold' disease. These results were the first real evidence that treatment could improve the outcome in ROP. Based on the results and recommendations of that study, we set up a screening service for ROP based at the Mersey regional neonatal intensive care unit. This unit comprises 24 cots, of which seven have been designated as being for infants who require ventilation. In practice these numbers are often exceeded. The purpose of this paper is to describe the service which started in April 1989.

Screening programme

Our aim was to screen all infants of birth weight below 1500 g and/or less than 32 weeks' gestation. Babies born at 26 weeks' gestation and under were first examined at 32 weeks after conception. Others all had a first eye examination by the time they were 7 weeks old, and in many cases it was before that. All infants were then examined every two weeks. If no ROP was detected by term, when the retinal vessels have normally reached the ora serrata, the babies were discharged. All babies who developed ROP continued to be reviewed by one of us (DIC) until there were either definite signs of regression or treatment by cryotherapy was indicated. Infants with mild ROP and those in whom regression occurred were reviewed until they were 3 years old, first at three monthly and then at increasing intervals. Orthoptic assessment, refraction, and retinal examination were performed. Infants who were treated with cryotherapy were seen more frequently because of an increased risk of developing high myopia, amblyopia, or strabismus. We intend to continue to follow up these children.

All neonatal units in the Mersey region were contacted and informed of the ROP screening service. They were invited to refer those babies who met the screening criteria to our unit for retinal examination if such a service was not already being provided by their local ophthalmology department. The offer was taken up by two hospitals in a neighbouring region and five of the seven nurseries which are located in the Mersey region, but outside Liverpool. One of us (DIC) already provided an ophthalmological service to the three nurseries in Liverpool.

During the two years of this study three babies were unfit to travel for screening. None had been previously nursed on our intensive care unit. On those occasions one of the authors (DIC) examined the babies in their respective neonatal intensive care unit.

Retinal examination is carried out as follows. The pupils are dilated with 0·5% cyclopentolate and 2·5% phenylephrine eyedrops, and ophthalmoscopy performed with a 28 dioptre lens. A lid speculum and scleral indentation is used to facilitate examination of the retinal periphery. Clinical findings are recorded in accordance with the recognised classification system.[2] All babies are monitored with a pulse oximeter and an electrocardiograph during the screening procedure. Most babies are examined on the neonatal intensive care unit in a converted isolation room modified by the fitting of blackout curtains. Those who were too ill to be moved were examined in their incubators. In these cases the view of the retina is less good because there is more light in the room. It is also more difficult to get the baby into an optimal position. In spite of these difficulties, these have often been the sickest babies with the worst disease, and even though the quality of the examination is less good, a quick look for 'plus' disease is possible.

Results of the screening programme

Between April 1989 and April 1991, 204 babies completed the screening programme, of whom 44 were transferred from other hospitals; 103 (51%) had developed ROP. Seventy five of the 91 babies (82%) born at 28 weeks' gestation or less developed ROP, while 28 of 104 babies of 29–31 weeks' gestation (27%) developed ROP. The incidence of ROP by gestation is shown in fig 1. All babies under 27 weeks' gestation developed ROP. Fifty two (87%) of the 60 babies with a birth weight of less than 1000 g developed ROP whereas 51 (35%) of the 144 babies of birth weight greater than 1000 g developed ROP. All 13 babies of birth weight below 750 g developed ROP (fig 2).

The worst stage of disease seen in either eye of the 103 babies with ROP is shown in table 1. Three babies were bilaterally blind due to retinal detachment (stage 4/5) when they were first examined by an ophthalmologist. Their clinical details are shown in table 2. This was at the start of the screening programme and they had been considered to be too ill for ophthalmological examination. We now make strenuous efforts to

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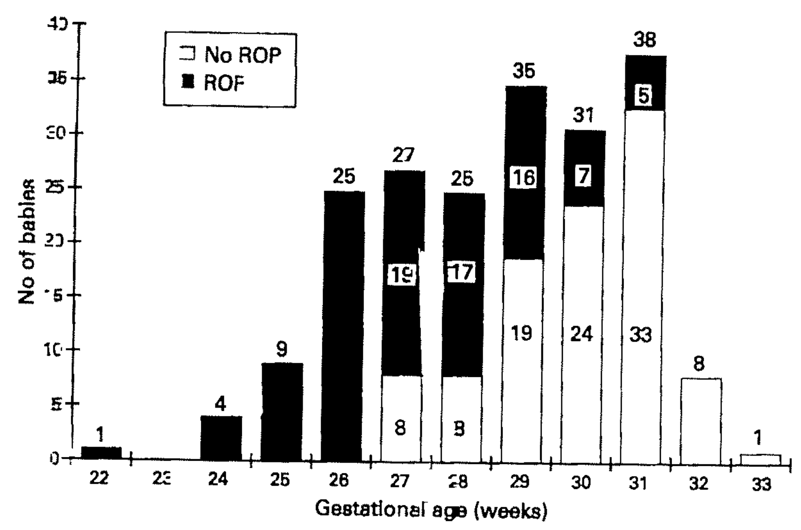

Figure 1 Incidence of ROP by gestation.

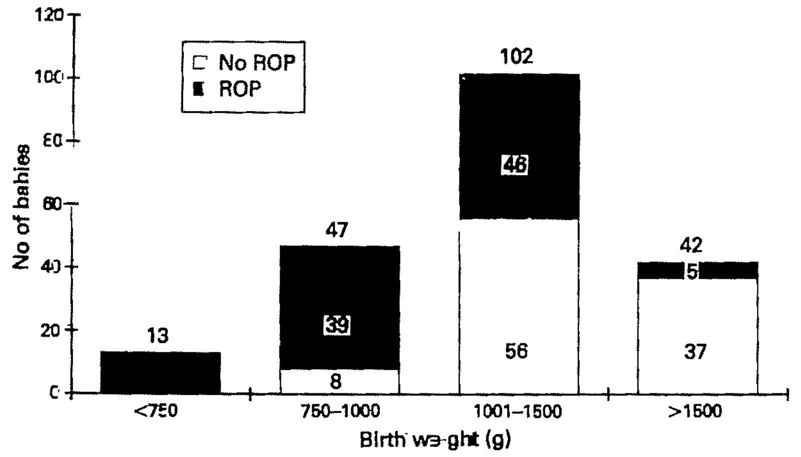

Figure 2 Incidence of ROP by birth weight.

review infants on time and the problem has not arisen since.

As all cases of stage 1 and stage 2 ROP regress spontaneously we have grouped these babies together and compared them with those whose worst stage of ROP was stage 3–5, plotted against gestational age (fig 3) and birth weight (fig 4).

Minor changes in heart rate occurred relatively frequently during scleral indentation, but there were no serious bradycardias. The major complication noted during ocular examination was apnoea. This occurred in three infants: one experienced recurrent apnoeic attacks both before and after the screening procedure; a second had chronic lung disease which subsequently required home oxygen; and the third baby was found to be anaemic (haemoglobin concentration 80 g/l) and a further examination after transfusion was uncomplicated.

Table 1 Worst stage of ROP achieved by either eye

	No of babies	Birth weight (g)		Gestation (weeks)	
		Median	Range	Median	Range
Stage 1	24	1271	595–660	29	26–31
2	44	1022	580–605	27	24–31
3	25	860	450–460	26	22–29
4/5	10	812	664–480	26	24–29

Table 2 Clinical details of three infants who had retinal detachment when first examined by an ophthalmologist

Gestation (weeks)	Birthweight (g)	Age first examined (weeks)	ROP stage
24	668	14	Bilateral 5
25	664	13	Bilateral 4
29	1480	24	Bilateral 5

Treatment by cryotherapy

Thirty eyes (16 babies) had stage 3 'threshold' disease and were treated with retinal cryotherapy. The median gestational age of these babies was 26 weeks (range 24–29 weeks), median birth weight was 813 g (range 622–1460 g), and median postnatal age at the time of treatment was 78 days (range 66–106). The treatment was performed on the neonatal unit with a paediatric senior house officer and neonatal nurse in attendance. The babies were intubated, ventilated, and nursed under an overhead heater. They were paralysed with pancuronium, and fentanyl (15 m/kg) was given for analgesia. Twenty six eyes were treated with a retinal cryoprobe to be avascular retina (average applications 37), four eyes were treated with the modified hammerhead cryoprobe. If necessary the conjunctiva was incised to allow better access of the cryoprobe over the avascular retina.

No anaesthetic complications occurred. Three eyes developed ocular complications: two were found to have a 1 mm overgrowth of conjunctival tissue onto the peripheral cornea, which was visually insignificant and occurred in one case despite conjunctival suturing; another baby was found to have suffered a small vitreous haemorrhage, temporal to the macula, at the time of the first post-treatment examination.

The outcome of treatment was regression of the disease in 21 of the 30 eyes, while seven eyes progressed to retinal detachment, and two eyes had retinal folds involving the macula. Three of the treated babies became bilaterally blind and were placed on the blind register. Subsequently, two of these three babies died as a result of other systemic illness unrelated to the ocular treatment. A further baby died with failed surgery in one eye, the other eye having been successfully operated on.

The estimated costs of this service are described below. This should not be considered to be a rigorous costing exercise. We have purposely left out the cost of the paediatric registrar and senior registrar, and the extra secretarial time required, because the people were already employed to work on the neonatal unit.

The initial capital costs for establishing this service was approximately £6000 for the purchase of the equipment. This included a cryotherapy machine, cryoprobes, an indirect ophthalmoscope, and lenses for the retinal examination. It did not include the cost of the pulse oximeter or a heart rate monitor.

The revenue costs of running such a service in terms of consultant ophthalmologist's time and extra nursing may be expressed as follows. Liverpool Maternity Hospital is a level 3 regional neonatal intensive care unit ventilating around 200 babies each year. This amounted to 2198 ventilator days in 1990 and 1894 ventilator days in 1991. At that hospital, one consultant oph-

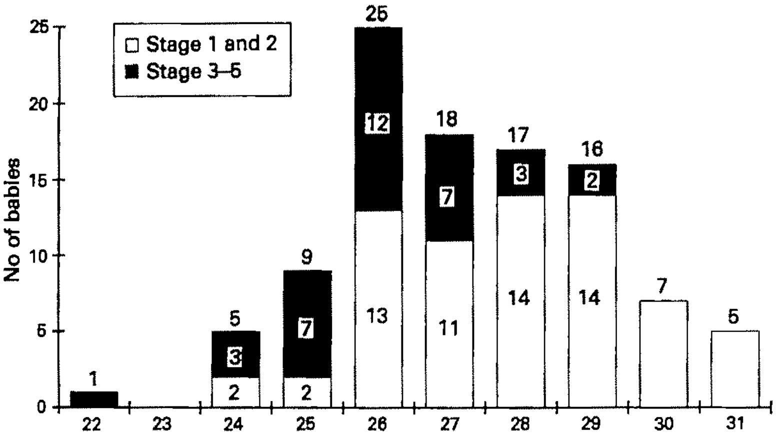

Figure 3 The worst stage of ROP (either eye) plotted against gestation.

thalmologist needed one notional half day (NHD) each week for screening. A further 1 NHD was needed for long term follow up of babies born prematurely at that hospital. This is carried out at the local eye hospital. A third NHD was required for treatment. A senior registrar in ophthalmology rotates through this service, but is considered supernumerary. An additional three half days of nursing time were needed for the service.

So that other neonatal units can determine their requirements for ROP screening based on the workload in their own unit, the revenue costs have been expressed in terms of the number of ventilator days per year. We calculated that the provision of the service required 1·2 NHDs of consultant ophthalmologist's time and 4·8 nursing hours each week per 1000 ventilator days per year. The average cost for the ambulance service to transfer the babies from the district general hospital to the central hospital was £15 per journey (£0·58 per mile and £18 per hour). No extra nurses were employed for this.

Discussion

One hundred and three (50%) of the 204 infants who satisfied the inclusion criteria for screening, that is who were below 32 weeks' gestational age and/or weighed less than 1500 g at birth and who completed the screening programme, developed ROP. This figure is similar to other published series,[3 4] but somewhat higher than the figure of 32·6%[5] reported in a recent study from the Hammersmith Hospital, London. Different inclusion criteria and examination techniques may account for the different rates of ROP found. We used a lid speculum and scleral indentation. This allowed us to examine the peripheral retina in greater detail than the method used by the Hammersmith group.

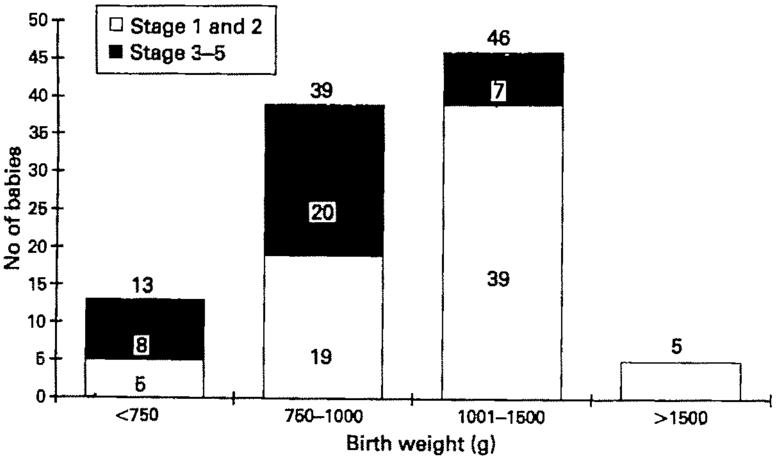

Figure 4 The worst stage of (either eye) plotted against birth weight.

ROP was more likely to occur in the more immature infants (82% of those born at ≤28 weeks) and in those with a lower birth weight (87% of those born <1000 g). In particular, the more serious and vision threatening stages of ROP—that is, stages 3–5—were seen in the more preterm infants (table 1). Twenty five babies (24%) developed stage 3 ROP, which is similar to or slightly higher than previous studies[3 5–7] and 10 babies reached stage 4/5 (nearly 10%). Figures 3 and 4 show that the severer stages of ROP are more common with decreasing birth weight and gestational age. Six out of 13 (46%) of babies born weighing under 750 g and nine out of 47 (19%) of babies weighing between 750–1000 g developed stage 3 threshold disease or worse. Such a high incidence of severe stage ROP is a matter of concern and is under investigation at present.

In 1988, the preliminary results of the randomised cryotherapy trial for stage 3 threshold ROP found that treatment reduced the likelihood of an unfavourable outcome from 43% for untreated eyes and 22% for treated eyes.[1] An unfavourable outcome was defined as 'posterior retinal detachment, retinal fold involving the macula, or retrolental tissue'. However, a more definitive follow up report from that same trial, published in 1990, found an unfavourable outcome in 51% of untreated eyes as against 31% for treated eyes.[8] Our results of cryotherapy treatment are more in line with the second of these reports. Nine of the 30 treated eyes (30%) in our group had an unfavourable outcome after cryotherapy.

Despite the apparent reduction in unfavourable outcome after cryotherapy, the relatively high proportion of cases that went on to retinal detachment is a cause for concern. Recently published results of cryotherapy for stage 3 ROP, performed earlier than the 'threshold' disease definition used by the Multicenter Trial of Cryotherapy for ROP[1 8 9] found that retinal detachment occurred in only 1·25% of 79 treated infants.[9] We feel that delay in cryotherapy by even a short time once threshold disease has been reached may be prejudicial to the outcome.

Complications during screening and treatment were fairly uncommon, mostly related to the stimulation of the oculocardiac reflex due to ocular manipulation and the administration of the eye drops.[10 11] No anaesthetic complications occurred during or after the retinal cryotherapy procedure. A vitreous haemorrhage was noted in one eye at the first post-treatment retinal examination. This complication has been reported to occur in up to 20% of treated eyes,[8] and may be due to the disease process itself rather than to the treatment.

We have presented the costs of the service in terms of the workload of the neonatal unit, the initial capital costs for equipment and the revenue consequences. Any attempt to cost blindness would be extremely difficult and would have to take into account the emotional as well as the financial costs involved for both the patients and parents.[12] Nevertheless a North American study has estimated that cryotherapy for ROP gives a 20 to 60 million dollar net savings to the Federal budget for each annual birth cohort of 25 000 premature infants (<1500 g), depending upon the assumptions made about lifetime costs of blindness.[13]

We conclude that screening for ROP should be available for all infants born at less than 32 weeks' gestation and weighing less than 1500 g, and that this should be performed by a trained ophthalmologist. If ROP of stage 3 or worse is detected, we recommend that treatment should be performed at a regional centre, where appropriate expertise will have been developed.

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PERSONAL PRACTICE

The unreactive fetal heart rate

J S Smoleniec, D K James

The 'flat' fetal heart rate (FHR) trace both before and during labour is viewed ominously by many obstetricians and midwives. The current medicolegal climate relating especially to care in labour is such that much emphasis is placed on an unreactive FHR. There is a tendency to link an unreactive FHR with an adverse outcome. However, it is only in a minority of cases that this is true. Furthermore, there is a wide variation in both definition and interpretation. Like many aspects of pregnancy care, the unreactive FHR is an example of 'a little knowledge being a bad thing'.

Definition

There is no agreed definition of an unreactive FHR; there is more agreement about what constitutes a reactive FHR. Therefore the simplest definition of an unreactive FHR might be one that fails to meet the criteria for a reactive FHR. A reactive FHR is one which has at least two accelerations of at least 15 beats per minute (bpm) amplitude (some would use 10 bpm[1]), each lasting for at least 15 seconds, during a set time period, on which there is no general agreement, but it varies from 10 to 120 minutes.[2 3] From the results of fetal behavioural studies[1] we use a 15 bpm amplitude of acceleration on at least two occasions in association with fetal movements within 40 minutes as our definition of reactivity in the fetus of 30 weeks' gestation or more, and consider 10 bpm to be more physiological at under 30 weeks (see below).

The problem with defining an unreactive FHR as one with no accelerations is that it does not take into account baseline FHR variation. There are two types of variation: short and long term. Short term variation is the variation in successive beat-to-beat intervals of the FHR. However, this variation cannot be accurately measured using external FHR monitoring via Doppler ultrasound with autocorrelation. Even when true beat-to-beat variation is accurately recorded using a fetal scalp electrode in labour, this cannot be visually quantified by someone observing the FHR. This is not surprising since the true mean (SE) beat-to-beat variation is 2·1 (0·2) ms.[4] In the clinical setting the only method of quantifying short term FHR variation is by using computerised FHR analysis. However, even when this is available it appears that beat-to-beat FHR variation is not as clinically useful as when beat-to-beat intervals are averaged over 1/16th of a minute and the difference between consecutive 1/16th of a minute intervals are used.[5]

Therefore it is long term FHR variation which is most commonly referred to in clinical practice. Long term variation is a visual assessment of the irregular oscillations of the baseline FHR. The normal amplitude of variation of the FHR baseline is commonly accepted as being between 5 and 15 bpm,[6] though some maintain that 25 bpm is a more realistic upper limit.[7] The considerable interobserver and intraobserver variation in interpretation and quantification of FHR variation has led to the introduction of computerised FHR analysis.[8]

Although theoretically computer analysis of FHR would appear to be the panacea for problems of FHR interpretation, it is only as good as the program criteria. Such criteria need to be validated over tens of thousands of pregnancies if they are to detect fetuses at high risk of intrauterine compromise. This point is well illustrated by a sinusoidal FHR with pathologically low FHR variability, being computed as having normal long term variation, which could only be diagnosed as abnormal by including a computation for short term variation.[9] It is noteworthy that the computer criteria for long and short term variation (evolved by comparing the analysis of thousands of FHR recordings with the subsequent infant outcome) differ remarkably from those used clinically. Furthermore, although computer analysis appears to detect antepartum fetal hypoxia in small for dates fetuses, the same criteria were not found to be applicable in labour.[10] Although promising, computerised analysis needs further evaluation.

In clinical practice we suggest that an unreactive FHR should be defined as an FHR which fails to demonstrate accelerations (at least two periods of 15 seconds' duration with 15 bpm or more for pregnancies of more than 30 weeks, and 10 bpm for pregnancies less than 30 weeks) in association with fetal movements during 40 minutes' continuous recording. If the FHR fails to fulfil these criteria after 40 minutes of continuous recording then it should be regarded as abnormal. This conclusion would be reinforced by the demonstration of FHR baseline variation persistently being less than 5 bpm during the 40 minutes. The presence of decelerations of the FHR (a fall of at least 15 bpm lasting for at least 10 seconds) would be further evidence of patho-

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logical FHR pattern. However, it must be remembered that decelerations of the FHR are a normal feature of the very immature FHR[1] and are therefore less likely to be pathological before 28 weeks.

It is our view that this definition of the unreactive FHR with the caveats relating to baseline variation and decelerations is equally applicable to antepartum and intrapartum recordings of the FHR.

Causes

The normal FHR recording is determined by the dynamic interplay of the autonomic nervous system, cerebral centres, and cardiovascular reflexes.[11] The autonomic innervation of the heart is the most important mechanism in controlling FHR variation. The parasympathetic muscarinic cardiodecelerator activity (producing a decrease in FHR but increased variation) is of primary importance in influencing beat-to-beat variation because of its rapid effect on FHR. In contrast sympathetic cardiac stimulation (producing an increase in FHR and decreased variation) leads to a much slower FHR response.[12]

The causes of unreactive FHR can be broadly divided into physiological and pathological (table 1).

PHYSIOLOGICAL

Gestation is the most important physiological influence on FHR. The FHR fails to manifest accelerations in association with movements and is thus normally unreactive before 24 weeks.[1] From 24 weeks onwards, FHR accelerations are seen for a greater proportion of the time although these are not normally of 15 bpm or more until 30 weeks onwards.[1] Over the last trimester fetal rest/activity cycles become manifest and these evolve into sophisticated fetal behavioural states from 35 weeks.[13] During the last trimester the commonest reason for an unreactive FHR is fetal quiescence or fetal behavioural state 1F.[13] At term a fetus can spend 30–40% of the time in quiescence and the average (SD) continuous period spent in quiescence is 21 (8·6) minutes.[14] Therefore we would recommend that an unreactive FHR should be investigated if quiescence lasts longer than 40 minutes.

Table 1 Causes of an unreactive FHR

	Physiological	*Pathological*
Fetal	Immaturity	Central nervous system Anomalies (for example anencephaly) Infection (for example varicella) Hypoxia
	Rest/activity states, 1F behavioural state,* or quiescence	Chronic (for example placental insufficiency, pre-eclampsia) Acute (for example intrapartum asphyxia, placental abruption or maternal cardiorespiratory collapse resulting in brain death) Cardiovascular system Arrhythmias Anomalies Cardiac failure (various causes)
Maternal	Diurnal variation External stimuli	Accidents (for example cardiorespiratory arrest) Drugs Opiates Anaesthetics (for example epidural) Parasympatholytic Sympathomimetic Magnesium sulphate

*Four categories of behavioural states are used to describe the fetus and these are numbered 1 to 4 and the letter 'F' is added to differentiate fetal states from neonatal states Behavioural states are determined by heart rate, fetal gross body movements, and eye movements. For example, state 1F, which is synonymous with fetal quiescence, is characterised by absent eye movements, a stable fetal heart rate with low baseline variation, which can be interrupted by isolated heart rate accelerations which are strictly associated with brief gross body movements, mostly startles.

Another normal feature of advancing gestation is the effect on baseline variation. Early in the second trimester variation is very slight (less than 5 bpm) but gradually increases as pregnancy progresses so that it is usually greater than 5 bpm after 26 weeks.[1] The mean baseline variation is approximately 7 bpm at 34 weeks. Thereafter the mean baseline variation depends on the state of activity of the fetus: in quiescence, the mean variation falls to reach 4 bpm at 40 weeks, whereas in activity variation continues to rise to about 10 bpm at 40 weeks.[1] Other fetal factors which are associated with an increase in FHR variation include fetal breathing and fetal mouthing movements.[1 15]

Maternal physiological factors which influence FHR reactivity include diurnal variation (more fetal activity and hence reactivity in the evening[16]) and glucose ingestion (increases fetal breathing and baseline variation).

External stimulation (for example, with vibratory or acoustic stimulators) of the fetus increases reactivity of the FHR and has been claimed to affect fetal behaviour generally.[17]

PATHOLOGICAL

A number of different pathologies can produce an unreactive FHR by directly affecting the fetal central nervous (CNS) or cardiovascular systems (CVS). Examples of pathologies directly affecting the CNS are structural abnormalities such as anencephaly, infections such as varicella, acute hypoxia (secondary to uterine contractions in labour, or placental abruption) and a major non-fatal hypoxic or anoxic insult[18] causing brain death such as placental abruption or maternal cardiorespiratory collapse.[19] The pathophysiological effect of chronic placental insufficiency as seen with severe pre-eclampsia or recurrent placental bleeding is to cause hypoxia which affects FHR variation.[20] In such cases when decompensation occurs there will be a resultant progressive reduction in FHR variation which will nearly always be accompanied by recurrent late or variable deceleration.[21 22] This effect has been shown by cordocentesis to be associated with fetal hypoxia.[23] If the decompensation continues, hypoxic acidosis will result which is characterised by loss of accelerations, decreased baseline FHR variation (<3 bpm) and shallow decelerations in response to Braxton Hicks' contractions.[24 25]

The commonest CVS cause for an unreactive FHR to cardiac arrhythmia. This can be primary idiopathic (supraventricular tachycardia, atrial flutter), or secondary to a structural cardiac abnormality. Cardiac failure in the fetus (secondary to anaemia, abnormal karyotype, cardiac anomaly or arrhythmia) also results in a unreactive FHR but this is probably due to the resulting hypoxia.

Maternal 'pathological' causes of an unreactive FHR are primarily confined to the effects of drugs taken by the mother, which cross the placenta and affect the fetal CNS and CVS. Those that predominantly have their effect on the CNS[26] include opioids such as pethidine, hypnotics such as diazepam, and anaesthetics both general and regional (epidural, spinal). However, the effect of an epidural or spinal anaesthetic in producing an unreactive FHR may be more commonly due to an effect on uterine perfusion. Drugs with predominant effects on the fetal CVS include parasympatholytic agents, such as atropine and tricyclic antidepressants, sympathomimetic agents such as ritodrine and salbutamol. Other drugs include magnesium sulphate and even paracetamol.[27]

A rise in maternal temperature will result in a rise in the FHR baseline with a reduction in variation, but accelerations tend to be preserved.

It should be stressed that not all these pathological causes of an unreactive FHR are confined to labour. Indeed the majority predate labour onset. This observation leads to the speculation that at least some of the unreactive FHR records which are identified in labour may reflect some longstanding problem which has not been identified because no FHR recording was undertaken before labour (for example undiagnosed intrauterine growth retardation).

Management of an unreactive FHR

ANTEPARTUM

The first principle of management when an unreactive FHR is reported or suspected is to ensure that the strict criteria for definition are fulfilled (see above) since the commonest cause will be fetal quiescence. The next principle of management is to try and ascertain the cause (table 2). A clinical assessment should be undertaken to exclude conditions such as pre-eclampsia, antepartum haemorrhage, drug taking, and a small for dates fetus. After this clinical evaluation, ultrasound fetal assessment is mandatory. A biophysical profile should be performed[28] which if normal is reassuring (which can be especially helpful in interpreting unreactive FHR below 28 weeks) but if it is abnormal it is associated with an increased risk of fetal compromise. In addition, during the profile procedure more critical observation of the relationship between the FHR and fetal activity may prove useful in diagnosing fetal pathology. For example, in brain death there is an unreactive FHR and absent fetal movement, whereas dissociation of fetal activity with an unreactive FHR is found with anencephaly and congenital abnormalities.[29]

Table 2 Management of an unreactive FHR

Ensure that the criteria for diagnosis are fulfilled to exclude physiological causes	
Unreactive FHR—need to exclude a pathological cause	
History and examination	Pre-eclampsia
	Antepartum haemorrhage
	Drugs
	Reduced/absent fetal activity
	Small for dates fetus
Ultrasound assessment	Biometry (fetal size)
	Anatomy CNS/cardiac
	Cardiac rhythm (M mode)
	Biophysical assessment
	Coincidence in fetal behaviour
	Fetal Doppler studies
	Stress/stimulation tests
Invasive testing	
Antepartum	Karyotype
	Viral serology
	Haemoglobin
	Blood gases
Intrapartum	Fetal scalp sampling
Treatment	
Antepartum	Fetal specific cause (for example antiarrhythmic drug or blood transfusion)
	Delivery

A detailed anomaly scan will help identify fetuses with obvious CNS, CVS, and karyotypic abnormalities. Cardiac arrhythmias should be categorised using M mode ultrasound. Fetal size assessment is important in diagnosing intrauterine growth retardation which is a common feature of many of the pathologies associated with an unreactive FHR. Similarly, abnormal Doppler ultrasound studies of the umbilical artery (increased systolic to diastolic ratio or absent end diastolic frequencies) are found in many conditions which can result in an unreactive FHR. Indeed the combination of intrauterine growth retardation, abnormal Doppler recordings, and an unreactive FHR is associated with a poor prognosis for the fetus.[30]

Fetal stimulation has been used as an adjunct to FHR monitoring in order to assess fetal wellbeing. The oxytocin stress test is commonly used in North America if the FHR is unreactive. However, it is not without risks such as aggravating fetal compromise and preterm labour. An alternative stimulation test is vibroacoustic stimulation which has been found useful antenatally in shortening the time to achieve a reactive FHR.[31] However, to date whereas a positive response is reported as reassuring (associated with a non-acidotic fetus), it is less useful in identifying fetal distress.[32] Furthermore, there have been suggestions that vibrocoustic stimulation may be potentially hazardous to an already compromised fetus.[33]

If the cause is still not certain then invasive testing may be necessary. In the antepartum period the diagnosis of chromosomal abnormality is the commonest indication for invasive testing, especially if ultrasound stigmata of anomalies are identified. While fetal blood sampling will provide a relatively quick answer, within two to three days, allow haemoglobin and blood gas and acid–base estimation (in case of fetal hydrops), and serological screening for viral infections, it is not without significant risk to the fetus especially in the growth retarded fetus.[34] Chorionic villus sampling may prove to be safer and quicker and the results as reliable. The relative merits of the two approaches have not yet been tested in controlled studies. Antepartum definitive treatment will depend upon the cause. If investigations conclude that the fetus does not have a lethal irreversible cause for the unreactive FHR or one which can be safely treated in utero (for example antiarrhythmic therapy[35] or fetal blood transfusion) then delivery is the usual treatment, often by caesarean section.

INTRAPARTUM

In labour while clinical assessment in order to determine the cause is still possible and should be undertaken, the full range of investigations may be neither available nor feasible. In practice the commonest investigation employed is fetal blood pH estimation obtained by fetal scalp sampling (which has an added advantage of acting as a stimulation test). However, there are limitations to this approach. Unless detailed fetal assessment has been undertaken before the onset of labour (for example as part of the admission assessment), management in labour is going to be largely on the basis of fetal acidaemia so that fetal normality before labour has to be assumed. This assumption may be proved to be incorrect once the infant is delivered. Furthermore, a normal scalp pH in the presence of an unreactive FHR does not exclude pathology.[36]

In labour, general fetal resuscitational measures should be employed even when the scalp pH is low since the cause of the unreactive FHR and decelerations maybe secondary to reversible causes such as cord compression or hypertonic uterine contractions or uterine hypoperfusion after epidural anaesthesia. The advantages are that in utero resuscitation is more efficient than neonatal resuscitation and an operative delivery may be avoided.[37] These measures may include stopping an oxytocin infusion and/or administering tolcolytics, fluid infusion, changing the mother's position to avoid caval compression, and giving facial oxygen. If these measures are unsuccessful, vaginal delivery is not imminent and the scalp pH is <7·2, delivery by caesarean section should be performed.

Conclusion

When faced with an unreactive FHR it is important that the criteria for diagnosis are fulfilled. The majority of so called 'unreactive FHR traces' are only such because FHR monitoring has not been continued for long enough. In the antepartum period an unreactive FHR should be investigated as quickly as possible. In labour the options are more limited and testing for fetal acidaemia is commonly the only investigation possible. However, it must be remembered that an intrapartum unreactive FHR may be caused by antepartum pathology.

Prompt delivery is the usual therapeutic option if the cause of the unreactive FHR is thought to be pathological, the effects on the fetus reversible and non-lethal.

At present there is no objective assessment of FHR other than by computer analysis which if used serially may enable management of an unreactive FHR in the antepartum period to be improved.

For the future, research should first concentrate on improving the understanding of the pathophysiological processes which ultimately lead to an unreactive FHR both antepartum and intrapartum. Secondly, efforts should be directed towards extending the range of investigations which are available, especially in labour, to obtain a more comprehensive picture of the fetal condition.

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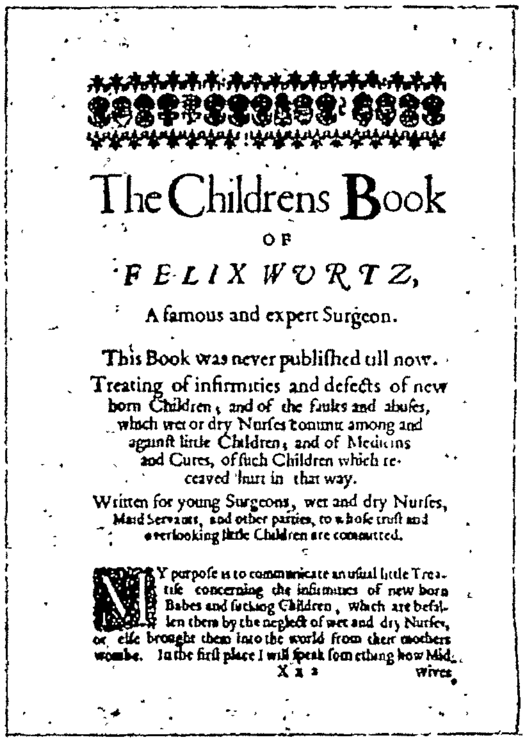
PERINATAL LESSONS FROM THE PAST

Felix Würtz of Basel (1518–75) and clubfeet

Peter M Dunn

Felix Würtz, the son of a surgeon in Basel, studied in Nuremburg before returning to practice in his home town. His paediatric treatise, first published in 1563,[1] was translated into English in 1656 as *The Childrens Book of Felix Würtz* (figure). It is clearly based on his own experience and is amazingly fresh and free from the prejudices of the past. As he wrote: 'I presume not to write of things which I never had an experience of; those I leave unto wiser men'.

Würtz's book contains a great deal of sound and original advice, for instance, on the choice of midwife or wet nurse, on the importance of discovering why a baby was crying, and on the harm that might be done by tightly swaddling the baby, as was the custom at that time. He also warns of the danger of deformation should the baby be always carried on the same arm, or be made to sit or stand too early and too long. Indeed Würtz was the first author after Hippocrates to give advice on the management of congenital orthopaedic deformities. The following section entitled 'Of crooked and lame children, coming thus into the world' illustrates his practical experience and mastery of the subject. Above all he appreciated the importance of growth in addition to postural correction.



* * *

The Childrens Book

OF

FELIX WURTZ,

A famous and expert Surgeon.

This Book was never publiſhed till now.

Treating of infirmities and defects of new
born Children, and of the faults and abuſes,
which wet or dry Nurſes commit among and
againſt little Children; and of Medicins
and Cures, of ſuch Children which re-
ceaved hurt in that way.

Written for young Surgeons, wet and dry Nurſes,
Maid Servants, and other parties, to whoſe truſt and
overlooking little Children are committed.

MY purpoſe is to communicate an uſual little Treatiſe concerning the infirmities of new born Babes and ſucking Children, which are befallen them by the neglect of wet and dry Nurſes, or elſe brought them into the world from their mothers wombe. In the firſt place I will ſpeak ſomething how Mid-

X x 2 Wives

The Childrens Book of Felix Würtz (1518–75).

'It hapneth that a child is born with crooked feet, placed and pressed one upon another, and must go on the ancles if they can . . . they usually say that such lame births are caused by frights, strang sights, or by carelessness, which nurses have to answer for. These defects they say are incurable; it agreeth with that saying, no body maketh himself crooked. These idle pratings causeth and lazy people, pretending, if my lame child cannot be cured, why should I be at expences or taking of pains. It is a base and false excuse, because experience proveth it to be otherwise . . .'

'Let no man be neglective if his child be thus crooked, as not to ask counsel about it; though all be not recovered which are in such cases, yet many are cured, if not perfectly, yet may they be mended in some sort; the which I do demonstrate with examples. I have dressed a newborn child, and ordered it with splinters as I thought fitting, whose feet from his mother's womb stood so, that the child stood on the outside ancle, which with splinters I brought to right, and that child went as straight as any other'.

'Therefore observe whether that joint both bow and turn easily to the place where it should be, then bind it that way, and cure it. Some joints will easily turn and bow, but that is not enough; binding is for such a joint the better, the growing whereof bringeth forward the cure and not the bowing or setting; the bowing of it is good, but it is not all, but it must be set and laid right also, then the one helps the other, and the growth in time is brought on; though little amendment is seen in a week, moneth, or three moneths, yet a whole years time may produce something, and in time perfectness comes in'.

'No splinter must be too close applyed here, neither must they be bound too hard; if too hard, and the child cryeth out by reason of the pains it feels, then instantly tie it slacker, for such pains would cause great mischief: therefore bind such joints softly and gently, according to the place . . . You are to observe exactly, when there cometh into any joint, pains, redness, smartings, blewishness, or collositie, a swelling or the like symptome, then it is very hurtful and dangerous; for then you have bound it too hard, unbind it presently, the child's welfare lyeth therein, if not his life; . . . at the first you ought to bind it gently, then you may soon perceave whether you are or may proceed further and more hard in it . . .'

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'When you are to dresse a child's crooked joint, then take my red plaister, which groweth stiff and hard, sticketh closely, and as you measured your splinters, then take the plaister spread on a cloth, apply it on the splinters, that it may stick thereunto, and cover the splinter well in the inside, then that band holdeth fast; for it keepeth the splinters so fast together, as a saddle holds firmly which is glued together. The over-plus of the plaister, which goeth or runneth beyond the splinters, you cut off and spread the plaister there on the splinters . . . pulled not too hard but gently: it is better they be bound slack a whole week, than too hard one hour. Then apply your measured splinters, you need but two, and not three, four, or more, which other fractures require. Then bind this joint as it fitteth in the bowing, and let it rest thus bound ten or fourteen daies, as you see occasion . . . if the case be altered and mended, then your splinters and binders must be accordingly altered . . . I have often practiced it, and had good success therein: God be praised forever: Amen'.

1 Wurtz F *Practica der Wundartzney* Basel, 1563

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LETTERS TO THE EDITOR

Stillbirths and non-lethal abnormalities—a mechanism of death?

Sɪʀ,—While counselling parents who have experienced a stillbirth of either a chromosomally abnormal baby or one with non-lethal congenital malformation, we are often asked 'But why did the baby die?'

Why do fetuses with chromosomal abnormalities or congenital malformations that do not involve major cardiovascular or cerebral defects die in utero? It is scientifically inadequate merely to attribute death to the presence of any congenital malformation as only a select few of such malformations can obviously cause death in utero. The latter would include defects such as cerebral tumours and major cardiovascular abnormalities such as transposition of the great vessels, conduction system abnormalities, large septal defects, etc. Death in utero of fetuses with congenital abnormalities without any major organ defects as is the situation with some sex-chromatin abnormalities, trisomy 18, achondroplasia, spina bifida, duodenal atresia, unilateral pulmonary agenesis, etc is not so easily explained.

Studies have shown that chromosomal abnormalities are 10 times more frequent in perinatal deaths than in unselected liveborn infants.[1 2] This does not, however, explain the mechanism of death in utero as most of the chromosomal abnormalities detected in perinatal deaths are compatible with survival after birth and are not usually of the types seen in early abortions.[2]

In a study of fetal heart rate patterns in fetuses with congenital abnormalities, Garite *et al* showed a significant increase of heart rate abnormalities but no characteristic pattern that would specifically identify major congenital abnormality.[3] Macafee *et al* had found a high incidence of growth retardation (46%) associated with major fetal malformations.[4] This may suggest a form of uteroplacental insuffiency and Garite *et al* postulated that abnormal placentation probably accompanies abnormal fetal development despite lack of histological evidence in many cases.[3] The high early miscarriage rate seen with chromosomally abnormal conceptuses probably supports such a theory. Fetal cardiac and neurologic normalcy are perhaps necessary for coordination of adequate nutritive and respiratory placental exchange. This theory however, is not supported by the finding of symmetrically small for date babies with chromosomal abnormality associated with adequate liquor volume (K H Nicolaides, personal communication).

Amniotic disruptions and limb-body wall disruptions can cause both external and internal malformations that can often be difficult to differentiate from malformations due to a primary genetic cause.[5] This, however, leaves a legion of stillbirths in chromosomally and congenitally malformed fetuses where there is no obvious mechanism of death and counselling is therefore less than accurate.

Why do these babies die?

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Renal candidiasis in the preterm infant

Sɪʀ,—We read with interest the case report by Drs Rehan and Davidson of a preterm infant with systemic candidiasis and renal candida bezoar. They state: 'to our knowledge there has been no report of a neonate with candidal septicaemia and renal candidal bezoar who has survived without surgical intervention.'[1] We report a preterm infant with systemic candidiasis and candida renal abscess who not only survived with medical management alone but at the age of 13 months has normal renal function.

Case report

A boy was born at 25 weeks' gestation, weighing 840 g. He required prolonged ventilatory support until day 22 and also inotropes, two exchange transfusions, a long line for parenteral nutrition, and repeated courses of broad spectrum antibiotics for suspected bacterial sepsis. He also had bilateral intraventricular haemorrhages and developed arrested posthaemorrhagic hydrocephalus.

On day 45 there was generalised clinical deterioration with recurrent apnoeas and abdominal distension, requiring reventilation. A full infection screen was performed and antibiotics commenced. Three days later there was a palpable left kidney and *Candida albicans* was grown from a suprapubic urine and blood cultures. The cerebrospinal fluid showed no fungal growth and candida serology was negative.

Renal ultrasound showed a hydronephrotic left kidney containing large amounts of debris and a discrete fungus ball. The left kidney was non-functional on intravenous urogram. Antifungal treatment was commenced immediately using intravenous amphotericin and intravenous, then oral 5-flucytosine. Drug concentrations of the latter were monitored and in the therapeutic range. Perineal and oral nystatin were also given. Treatment was continued for a total of six weeks and was well tolerated. Plasma urea and serum creatinine concentrations remained normal throughout. There was close consultation with the paediatric surgeons—to intervene if the fungal debris persisted and the kidney remained non-functioning—but there was continued clinical, radiological, and functional improvement.

A dimercaptosuccinic acid (DMSA) scan 4·5 months later showed an anatomically normal left kidney contributing 40% of total renal function. Ultrasound revealed a little fullness of the left upper pole collecting system only. Subsequent blood and urine cultures remained sterile. General progress 13 months later remains entirely satisfactory with normal growth and renal function.

Systemic candidiasis is well documented in the very preterm and low birthweight infant with a reported incidence of 3–4% in those under 1500 g[2]—and an associated high morbidity and mortality. Insertion of indwelling intravascular catheters, provision of total parenteral nutrition, and administration of broad spectrum antibiotics are associated with an increased risk of systemic disease. In the neonate *C albicans* has a particular predilection for the kidneys and of those reported with renal candidiasis, most have been treated by nephrostomy drainage with both systemic and local antifungal therapy.[3] Outcome has largely been monitored in terms of survival and there is very little documentation of subsequent measurements of renal function in those who survive. Here then is an infant who has been successfully treated with systemic antifungals, without surgical intervention and at follow up has total resolution of his renal disease.

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Annotations

Drug abuse in children and adolescents: an update

Unlike cigarette smoking and alcohol drinking, there are no national surveys of drug abuse among children and adolescents in the UK. However, local small scale surveys and surveys of special populations from various parts of the UK indicate that 5–20% of school age children have 'ever tried' a drug with 2–5% using weekly or more often, and with a peak prevalence around the age of 14–16 years.[1] National American surveys usually report higher rates. Most dramatic in the USA is the increase in cocaine use: in 1985, over 1·1 million 12–17 year old adolescents had tried cocaine.[2] However, recent reports suggest that there may be some decline.[3] Overall about 5% of adolescent drug abusers in the USA meet the criteria for 'dependency',[4] with multiple drug abuse being the rule rather than the exception.[5]

The age at which adolescents start drug taking is getting lower: an average of 13–15 years. Girls are less likely to use drugs and start later than boys. Once they start, however, their use is more committed.[6] Earlier illicit drug abuse is often associated with heavier subsequent drug abuse,[7] more persistent abuse,[8] and the abuse of 'harder' drugs.[9] Furthermore, starting to abuse illicit substances before the mid-teens is more likely to be associated with later delinquency, severe psychiatric disorders, and antisocial problems.[7]

Drug abuse is notoriously influenced by social and cultural factors such as social milieu, availability and legislation. Although adolescents can be involved in the abuse of any drug, they tend to be more involved in the abuse of volatile substances, cannabis, amphetamines, hallucinogenic substances, and 'pills' such as tranquilisers and hypnotics. Drug abuse is commonly associated with higher rates of alcohol use and cigarette smoking.

Who is at risk?

Drug abuse should now be suspected in preadolescents as well as adolescents. It can account for the physical manifestations and psychological disturbances seen in many youngsters. There are some children who should be perceived as being 'at higher risk' of drug abuse: children of substance abusers, victims of physical, sexual or emotional abuse, school drop outs, pregnant teenagers, economically disadvantaged children, delinquents, and those with mental health problems.[4] Some 'relative risk factors' that would help in raising the level of suspicion of drug abuse were identified.[10] The most significant indicator is peer drug abuse. However, other factors such as truancy, conflict with parents, law infringements, misbehaviour at school, alcohol use, and cigarette smoking are also indicative. The level of suspicion is directly related to the number of risk factors present.

Psychopathology

The relationship between psychopathology and drug abuse is very complex and still poorly understood, and the mechanism by which the two interact has not progressed much beyond establishing associations. The complex nature of psychopathology during adolescence poses an added difficulty in studies in this area. Longitudinal studies are necessary to unravel the picture.

Drug abuse in adolescence is commonly associated with inappropriate sexual behaviour, delinquency, school and social misbehaviour, and poor academic performance.[11 12] Higher rates for psychosomatic complaints, anxiety, interpersonal conflict, social dysfunction,[13] depressive symptoms,[14] and suicide[15] were reported among drug abusers. This led to the suggestion that drug abuse may, indeed, start as a form of self medication to relieve emotional distress.[16] Swadi carried out a cluster analysis of 46 referred adolescent drug abusers and found that there were three groups.[17] First, there was a behavioural dysfunction group making 76% of the sample, consisting mainly of boys, with an average age of 14 years with high rates of behavioural problems and adverse family dynamics. Almost half of them also showed depressive symptoms. Second was a family dysfunction group making 16% of the sample, consisting mainly of boys, with an average age of 13·5 years, and an abundance of adverse family dynamics. To a lesser extent, they also showed a mixture of emotional and behavioural symptoms. Third, was a life events/emotional dysfunction group making 8% of the sample, consisting mainly of 15–16 year old girls who showed high rates of significant and adverse life events. They showed significantly higher rates of emotional (especially depressive) than behavioural symptomatology. No adverse family dynamics were reported in this group.

Physical manifestations

Drug abuse can account for many physical manifestations in adolescents. A detailed account of the physical effects of specific substances is beyond the scope of this review and available elsewhere.[18] However, drug abuse should be suspected when symptoms of sudden psychological change or deterioration of physical health are encountered, especially in particular groups of adolescents.[4] Abuse of volatile substances accounts for about 100 deaths each year in the UK.[15] Death usually results from anoxia, cardiac arrhythmias, respiratory depression, or trauma. Chronic abuse can cause symptoms of central nervous system depression, upper respiratory tract infections, persistent cough, and laryngitis and can cause cardiomyopathy, liver damage, or kidney damage. Stimulants such as amphetamines cause autonomic arousal, sleep disturbances, loss of weight, and in large doses, toxic confusional state. Cannabis often causes sweating, tachycardia, and peripheral vasodilatation. Opiates cause constipation, clouding of consciousness, nausea and vomiting, respiratory depression, and bradycardia. Some substances such as amphetamines and cannabis can cause toxic psychotic states, indistinguishable from schizophrenia.

The physical manifestations of a withdrawal syndrome are uncommon in adolescents because the syndrome of drug dependence itself is uncommon. If they occur, withdrawal symptoms depend on the type of substance abused. For example, gastrointestinal and 'flu'-like symptoms occur in opiate withdrawal; central nervous system excitability and even convulsions in barbiturate withdrawal; and lethargy, depression, and poor concentration in stimulants withdrawal. Cocaine withdrawal causes psychological rather than physical symptoms

Course and outcome

The majority of adult 'addicts' start in their teens,[20] but it is not yet possible to describe the 'course' of adolescent drug abuse accurately, Only a small proportion 'progress' to addiction. A natural 'maturational process' was suggested as a most likely outcome for most adolescent abusers.[21] Those who do not 'mature out would eventually form the core of future adult addicts. However, it is not yet possible to predict with confidence who would mature out. Some suggest that a conventional social role and a social context unfavourable to drugs predict early cessation Furthermore, the degree of prior abuse and peer abuse of drugs are influential in future abuse. Those who abuse drugs for psychological reasons are less likely to stop than those who abuse for social reasons.[21]

Untreated, drug abusers are at risk of continued (possibly dangerous) use and high rates of psychiatric and social problems,[22] with aggression, antisocial behaviour, occupational, and marital problems being most common. There is also the increased risk of HIV infection associated with the risky lifestyle drug abusing adolescents lead and the use of contaminated needles in some drug abusers. Adolescent drug abusers are more likely to have unprotected sexual intercourse after drug use.[23]

Future directions

Given the uncertainty about the course of drug abuse in adolescents, there has been a natural shift to put more emphasis on prevention. The 'epidemic nature of drug abuse suggests that prevention should be both primary (prevention of initiation) and secondary (prevention of progression to more hazardous patterns and continuation into adulthood).

There is an increasing recognition that secondary prevention in the form of treatment is necessary. Current counselling services have a useful but inadequate role as there is much more to the treatment of drug abuse than counselling. Adult treatment services are by nature and design not suitable for adolescents. Special treatment facilities for adolescents have gone a long way in the USA but are virtually absent in the UK. There is a good case for special services given the extent of the problem and its specialist nature.

It is now well established that drug education, in many of its known forms, is ineffective with only very modest results at best.[24] In view of the increasingly younger age of initiation into drug abuse, there is a strong case for introducing drug abuse prevention programmes at a younger age. That would require a rethink of prevention strategies with a move away from the didactic instructional methods currently employed and the adoption of a holistic approach towards the issue of health and behaviour in adolescents. Ideally, prevention should aim at total abstinence. However, as second best it may be useful to delay the onset of regular drug use as much as possible; this would spare the adolescent some of its worst effects in terms of more dangerous patterns of use and psychological and social adverse consequences.

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Consent to treatment in childhood

The ability of children to give a legally valid consent to medical treatment has been a vexed one ever since the matter was addressed by Parliament in the Family Law Reform Act of 1969.[1] [2] This legislation, which was far from clear in its scope stated that a child could consent to medical or surgical treatment on attaining the age of 16 years, but said nothing as to the ability of children under that age to consent. Then came the case of *Gillick v West Norfolk and Wisbech Area Health Authority,*[3] a case which addressed the issue of whether doctors could prescribe contraception to a girl under the age of 16. The decision reached by the House of Lords in this case was that the provision of treatment to a child under 16 was legal, provided that the patient understood the nature of the proposed procedure. This was in line with an earlier Canadian case, which had linked the capacity of children to consent with the concept of individual ability to understand the implications of medical treatment. On the basis of the decision there came into existence a standard known as 'Gillick competence', which appeared to settle the matter, at least to an extent. Yet the Gillick test is not without its grey areas, and indeed the courts have continued to pronounce on the issue.

The basic outlines of the law of consent in this context are as follows:

(1) As far as consent is concerned, children are special for two reasons: they may not have the capacity to consent, and the wishes of parents have to be taken into account. A decision as to the medical treatment of a child under the age of 16 inevitably involves some consideration of parental wishes, even if parental views are eventually overridden.

(2) Children who are too young to understand the implications of treatment cannot give a valid consent to treatment. In the case of such children, the doctor must obtain the consent of the parent to the treatment proposed. If the parent consents, then the doctor is entitled to proceed with the treatment even if the child himself or herself objects to what is being done.

A, a 10 year old is admitted to hospital with acute abdominal pain. A diagnosis of appendicitis is made and A is informed that he must have an operation. A says that he does not want an operation and is adamant that nothing will be done to him. Once parental consent is obtained, treatment may proceed. If the parent is not available to give consent, hospital authorities are justified in such a case in proceeding on the basis of necessity, on the grounds that the operation cannot reasonably be delayed until the parent is traced or the authorisation of a court sought.

In this example, if the parent declined to give consent to the operation (for example, on grounds that a blood transfusion might be required and this offends the religious scruples of the parent, permission to perform the operation might be sought from a court). If there is no time for this to be done, and the matter is one of urgency, necessity justifies the carrying out of the procedure and the chances of a court ever holding this unjustified are effectively nil.

(3) The obtaining of parental consent to the treatment of children who are too young to give a valid consent themselves is important, and will normally be required, but there are cases where the wishes of the parent will not be the deciding factor. This may be so, for example, where a decision has to be made about the treatment to be given to a grossly handicapped or chronically sick infant. Here the fact that parents do not wish the child to be treated is not necessarily going to commit the doctor to a regimen which is calculated to do no more than palliate suffering. It may be that a parental veto of treatment in such a case should be ignored in the child's best interests, although doctors may be advised in such a case to seek court approval.

Over the last few years the courts have clarified the position in this sort of case, giving useful guidance to doctors involved in the treatment of infants in this category. The first of this series of case was that of *Re B,*[4] decided over a decade ago. B was a baby with Down's syndrome who required an operation for the removal of an intestinal blockage. The parents took that view that this was nature's way of dealing with the abnormality and declined to give consent to the operation. Medical evidence was put before the court that B's life expectancy was between 20 and 30 years, and the court decided to authorise the procedure on the grounds that these years were a life to which B was entitled, even if she was to live them under the shadow of mental handicap. The more recent case of *Re C,*[5] however, involved a very different prognosis. C at the time of the hearing was a 16 week old baby suffering from congenital hydrocephalus. The medical evidence put before the court was gloomy in the extreme: C would never develop any real intellectual ability; she would be unable to lift her head or communicate, and she was not expected to live to adolescence. In these circumstances the court authorised treatment that was directed only towards the relief of suffering and agreed that treatment for the prolongation of life was not required. C was a ward of court, and there was no conflict with parental wishes, but the case is none the less important in this context in that it demonstrates the sort of case where a parental decision not to authorise life prolonging treatment would be upheld. Parents do not have the right to deny treatment to children who have some prospects of at least some quality in their lives, but they do have a right to prevent a child from being treated in a way which will only prolong considerable misery. This has recently been further supported by the decision of the Court of Appeal in *Re J*[6] in which an unsuccessful attempt was made by the Official Solictor to seek a ruling that the denial of life saving treatment was never justified where a child had been made a ward of court, even if the life saving treatment would only serve to prolong a severely limited life.

(4) Where children have the ability to understand the nature and implications of medical treatment, their consent renders treatment legal. The assessment of competence is a matter for the doctor and obviously there will be room for doubt in individual cases. In determining whether a child is mature enough to consent, a doctor must bear in mind what a reasonably competent doctor in his position would be expected to decide in the situation. Thus a doctor who formed the opinion that an 8 year old—even an intelligent 8 year old—was capable of understanding the full implications of a surgical operation would be running a distinct risk. By contrast, a doctor who decided that an intelligent 15 year old girl understood the implications of chemical contraception would no doubt be widely supported. But what about the ability of a 13 year old girl to understand the implications of contraception? This is more controversial, but perhaps not so marginal as to make a medical assessment of capacity in such a case unlikely to be supported.

(5) Finally, there is the difficult case where a child under the age of 16 withholds consent to a medical procedure, although he or she would be judged to have the capacity to consent to it. This issue has now been raised before the

courts in *Re R*,[7] a case involving a 15 year old girl suffering from episodes of psychotic illness. The girl's refusal to continue with drug treatment, articulated during a period of lucidity, was overruled by the court on a variety of grounds. Lord Donaldson said in his judgment that where there was more than one person or body who could give consent, treatment would be vetoed only where *all those who could consent had refused to do so*. A parent has a right to consent to the treatment of a minor, and this right lasts as long as minority does (that is, until the age of 18 years). This would appear to suggest that a competent child (that is, a child capable of understanding the implication of what is being proposed) who declined treatment might still be treated legally if either the parent consents or the court exercises wardship authority and authorises treatment. The court in *Re R* point out, however, that the consent of the parent in such a case would not mean that the treatment *had* to be given; the minor's wishes should carry great weight in the doctor's decision making. This is rather difficult to square with current notions of adolescent competence, and indeed with the philosophy underlying the Gillick decision. For this reason it is possible that a future court, faced with such a conflict, would restrict the application of the principle suggested in *Re R* to those cases where (i) the rationality of the child is in doubt (and where there would therefore be doubt as to capacity), or where (ii) the child is considered too young to make an informed decision. There is no real difficulty in holding that a 14 or 15 year old who places his or her life in jeopardy by refusing treatment is too young to have the capacity to make a decision of that significance. This may be done on the grounds that a refusal of treatment requires a greater degree of capacity than the giving of consent does.

(6) Scotland is different, and the basic question of ability to consent is resolved in a recent statute. Under the Age of Legal Capacity (Scotland) Act, 1991, a child under the age of 16 may give a valid consent provided that, in the opinion of a medical practitioner, he or she is capable of understanding the nature and possible consequences of the procedure or treatment. Two points might be made: the determination of competence is left entirely to the doctor, and nothing is said about the case of a competent child who withholds consent. In the latter case, if there were a serious threat to the child's health, the courts would probably override the child's refusal on the grounds suggested above, namely that consent and refusal involve different degrees of capacity.

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Molluscum contagiosum

Molluscum contagiosum is a self limiting cutaneous viral infection, especially common in children. It produces characteristic pale papules, which usually cause little discomfort. Indeed for most patients, attempts at treatment and limitation of activities associated with spread of the infection may cause greater distress.

Molluscum contagiosum virus (MCV) belongs to the poxviridae; like other members of this family it is a DNA virus which replicates in the cytoplasm of the host cell and is especially adapted to epidermal cells. The only significant host is man and MCV cannot be grown in tissue culture or eggs. Restriction endonuclease analysis permits classification of MCV into at least two types, named 1 and 2, of which type 1 is much the commoner, but there is as yet no consistent evidence relating the virus type to the clinical appearance of the lesions or to their anatomical distribution.[1 2]

Epidemiology

Infection follows contact with an infected person or contaminated objects. It is assumed that epidermal injury facilitates inoculation of the virus, but infection of intact skin may also be possible. In hot countries, where close contact between lightly clad children is frequent, molluscum contagiosum is commonest in young children, the incidence peaking for example in Fiji between the ages of 2 and 3 years.[3] In more developed countries the infection is commoner in school age children and correlates with the use of swimming pools[3 4] although the precise mode of transmission in this situation is unknown. In a Japanese study involving over 7000 children, the incidence of molluscum contagiosum was 7·5% among swimmers and 3·6% among non-swimmers.[4]

In adults transmission between sexual partners is recognised, and such infections usually occur on genital, perineal, pubic, and neighbouring skin. Transmission of molluscum contagiosum to a child during sexual abuse must be possible in principle, but does not appear to have been recorded. Innocently acquired childhood molluscum contagiosum is often widespread and lesions are frequently seen on and near genital and perineal skin. Therefore sexual transmission of molluscum contagiosum to a child should be suspected only if there is other evidence of sexual abuse.

Immunity

Specific antibodies against MCV can be detected in the majority of infected patients, but their biological significance is unknown. The importance of cell-mediated immunity is inferred[5] from occasional reports of widespread infections in patients immunosuppressed by disease or on immunosuppressive treatment and especially those with HIV infection.[6] Atopic eczema and use of stronger topical steroids are sometimes associated with more widespread infections.

Natural history

The incubation period is estimated at between two weeks and six months, though the source of infection is seldom reliably identified. In the immunocompetent patient, individual lesions regress mostly within two months, although solitary lesions may persist for up to five years. New lesions may be due to virus acquired at the time of initial infection, but are probably more commonly due to autoinoculation. The whole infection clears usually within six to nine months, but occasionally persists for a few years. Lesions may appear after apparently successful treatment, and it is suggested that a lesion free period of four months should be required before the patient can be regarded as cured. Reinfection is possible but uncommon.

Clinical features

Molluscum contagiosum may affect any part of the skin surface, but it is rare on palms, soles, and mucous membranes. Lesions are typically spread over an anatomical region such as an axilla and adjacent arm and chest wall, or perineum and upper thighs, but sporadic lesions may be more widely scattered presumably due to autoinoculation. In patients with HIV disease and AIDS, multiple and refractory lesions are particularly common on the face.

The lesions of molluscum contagiosum are typically shiny, pale hemispherical papules, 2 to 5 mm across, often with a central pore or dimple ('umbilication'). Careful inspection may reveal tiny papules in adjacent skin, best seen with a hand lens. Larger lesions occasionally occur, especially if solitary. The clinical appearance is usually diagnostic. The expression of thick white ('cheesy') material from the centre of the lesion, for example by squeezing with forceps laid across the skin surface, would be corroboratory, but is seldom appreciated by young children. Atypical, usually solitary, lesions may be diagnosed histologically after curettage.

Resolution, spontaneous or after self induced or therapeutic trauma, proceeds through an inflammatory phase with erythema and crusting, often resulting in a small superficial scar. Disrupted lesions bleed, sometimes profusely. Eczema in adjacent skin is occasionally seen, and is commoner and more marked in those with atopic eczema. Conjunctivitis may accompany eyelid lesions.

Treatment

Affected patients should be advised to avoid contact sports, swimming pools, and shared baths and towels until the infection is clear.

Molluscum contagiosum lesions are vulnerable to physical damage; anything which disrupts an individual lesion will lead to its resolution. Scratching by the patient often helps in this way, although spread of the infection may occur. Superficial curettage, shaving with a sharpened wooden spatula, and expression of the body of the lesion by forceps, have all been used. Such methods are usually followed by an application of a silver nitrate stick, phenol, or strong iodine solution. Chemical methods alone, however, are seldom useful. If cryotherapy is available it is now regarded as the treatment of choice. Briefer freezes are required than for warts of a similar size. Because of the likelihood of subsequent development of further lesions, several treatment session two to four weeks apart should be anticipated. The degree of pain caused by this relatively gentle cryotherapy is variable, but it is unlikely to be tolerated by most children under 10 years of age. The prior use of a topical local anaesthetic such as EMLA cream containing lignocaine and prilocaine (Astra) often helps.[7] Large solitary lesions may be removed by curettage and diathermy after injection of local anaesthetic, permitting histology if required, but such lesions are rare in children. A weak, or occasionally medium strength, topical steroid may be used for associated eczema. Secondary bacterial infection may require an appropriate antibiotic.

In young children, especially if the molluscum contagiosum affects difficult sites such as eyelids, attempts at treatment may be frightening, and it is best in these circumstances to reassure the parents that the infection is not serious and will eventually resolve spontaneously.

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Effects of oral and intramuscular vitamin K prophylaxis on vitamin K_1, PIVKA-II, and clotting factors in breast fed infants

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Abstract

A randomised clinical trial was conducted to establish the effects of oral and intramuscular administration of vitamin K at birth on plasma concentrations of vitamin K_1, proteins induced by vitamin K absence (PIVKA-II), and clotting factors. Two groups of about 165 healthy breast fed infants who received at random 1 mg vitamin K_1 orally or intramuscularly after birth were studied at 2 weeks and 1 and 3 months of age. Although vitamin K_1 concentrations were statistically significantly higher in the intramuscular group, blood coagulability, activities of factors VII and X and PIVKA-II concentrations did not reveal any difference between the two groups. At 2 weeks of age vitamin K_1 concentrations were raised compared with reported unsupplemented concentrations and no PIVKA-II was detectable. At 3 months vitamin K_1 concentrations were back at unsupplemented values and PIVKA-II was detectable in 11·5% of infants. Therefore, a repeated oral prophylaxis will be necessary to completely prevent (biochemical) vitamin K deficiency beyond the age of 1 month.

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Vitamin K deficiency is associated with haemorrhagic disease of the newborn. Three patterns of bleeding have been differentiated: early haemorrhagic disease of the newborn within 24 hours after birth, classical on days 1 to 7, and late after the first week of life.[1] Late disease is often intracranial. These haemorrhages may be fatal or cause serious morbidity. Breast feeding has an important role in the pathogenesis of classical and late disease.[1] Many countries recommend vitamin K prophylaxis after birth to prevent this hazard of vitamin K deficiency. Nevertheless, there are still controversies concerning the best way of providing effective prophylaxis, resulting in different policies. The safety of oral and parenteral vitamin K prophylaxis in the prevention of classical haemorrhagic disease of the newborn has been established, whereas the relationship between a single vitamin K dose at birth and late haemorrhagic disease of the newborn has not been clearly determined.[1 2] Several studies have indicated that oral prophylaxis might be as effective as intramuscular administration, but these studies lack follow up beyond the first week of life.[3–5] Epidemiologically, intramuscular vitamin K prophylaxis appears to have a lower incidence of failure,[6–8] probably because of the more reliable absorption.[4] Oral administration has the appealing characteristics that an injection is avoided and that administration is simple, resulting in better parental acceptance.

The aim of this study was to evaluate whether oral administration of vitamin K is as effective as intramuscular administration in the prevention of vitamin K deficiency beyond the first week of life in breast fed infants. Determination of proteins induced by vitamin K absence (PIVKA-II) was used to detect biochemical vitamin K deficiency. Vitamin K is necessary for production in the liver of coagulation factors II, VII, IX, and X. The vitamin K dependent carboxylation of glutamic acid residues to γ-carboxyglutamic acid residues promotes calcium binding to these proteins which is essential for effective haemostatic function. When carboxylation is impaired because of deficiency or antagonism of vitamin K, inert precursors of prothrombin (factor II) are detected in the blood.[9] These are known as PIVKA-II. In formula fed infants and adults PIVKA-II is not detectable, but it is found relatively frequently in breast fed infants without vitamin K prophylaxis at birth.[10] Although biochemical markers of vitamin K deficiency are only of limited value in assessing clinical relevance, they provide a most sensitive way to determine which group of infants is at risk for haemorrhagic disease of the newborn.

Subjects and methods

A total of 331 infants, delivered spontaneously vaginally, in the University Hospital of Nijmegen or at home under midwife guidance, were enrolled. Inclusion criteria were: gestational age of 37 weeks or more, birth weight over the 2·3rd centile, and Apgar score of 7 or more at 5 minutes. The mother had to be healthy and not be taking vitamin K, anticoagulants, antibiotics, or antiepileptic drugs. All mothers intended to breast feed their child. After the parents had given informed consent the neonates received vitamin K prophylaxis on the first or second day of life. The newborns were randomly allocated to one of the two treatment groups. One group (n=165) received 1 mg vitamin K_1 orally (1 mg/ml phytomenadione, Konakion, Hoffman-La Roche). The other group (n=166) received 1 mg vitamin K_1 intramuscularly (Konakion 2 mg/ml). Some characteristics of the infants are represented in table 1. No feature was significantly different between the groups at the beginning or at other times during the study (χ^2 and Student's *t* test).

Table 1 Comparison of the two study groups of healthy breast fed infants; results are mean (SD)

	Oral group	*Intramuscular group*
No of infants	165	166
Sex (% male)	55·8	47 0
Gestational age (weeks)	39·8 (1 3)	40·1 (1 2)
Birth weight (g)	3424 (439)	3417 (440)
Apgar score at 5 min	9·7 (0 5)	9 7 (0 6)
Arterial cord blood pH	7·26 (0 07)	7 26 (0·07)
Age at vitamin K administration (hours)	19·9 (12 7)	13·6 (13 5)
Follow up assessments:		
Age at 1st venepuncture (days)	14 1 (1·2)	14 0 (1 3)
Age at 2nd venepuncture (days)	30·5 (1 8)	30 5 (1 8)
Age at 3rd venepuncture (days)	88·6 (5·6)	89 5 (5·6)

If the child was still exclusively breast fed, blood was sampled at 2 weeks and 1 and 3 months of age. In other words, when the mother stopped breast feeding follow up was terminated. A sample of 5 ml of blood was drawn by venepuncture and divided: 2 ml of citrated blood (in silicone coated tubes containing 10% (v/v) of sodium citrate 3·8%) and 3 ml of coagulated blood with no additive. After measuring blood coagulability (Thrombotest, Nijegaard and Co), the citrated blood was centrifuged (5000 rpm for 10 minutes) and the plasma stored at −70°C until coagulation parameters were determined. The coagulated blood was protected from the light immediately after sampling, centrifuged (3000 rpm for 5 minutes) and the serum stored at −20°C for vitamin K_1 determination. All samples were coded to provide blind analysis.

Activities of clotting factors VII and X were measured by chromogenic substrate assay, with substrate S2765 (Coa-set FVII kit, Kabi Diagnostica) and substrate S2337 (Coatest FX kit, Kabi) respectively. These methods are not sensitive to PIVKA factors.

PIVKA-II was assayed by an enzyme linked immunosorbent assay, using a monoclonal antibody previously described (Eitest mono P-II Eisai).[11] This antibody reacts with decarboxylated prothrombin (PIVKA-II) quantitatively and does not cross react with native prothrombin. PIVKA-II concentrations are expressed in arbitrary units (AU)/ml, so that 1 AU corresponds with 1 µg of purified prothrombin. In severe vitamin K deficiency PIVKA-II can amount to more than 20 AU/ml. The detection limit of 0·10 AU/ml was used as the upper normal limit, defining PIVKA-II concentrations higher or lower than that concentration as PIVKA-II positive or negative, respectively.

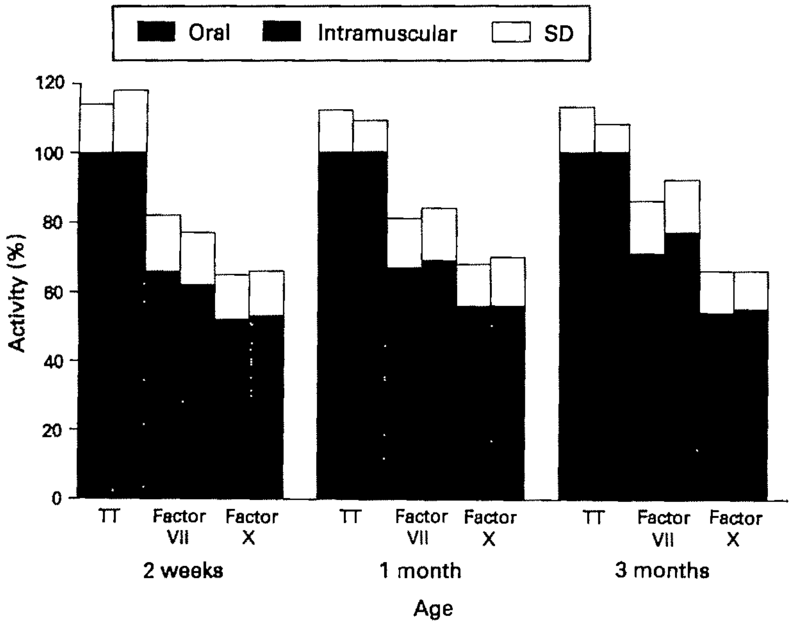

Figure 1 Median (SD) of blood coagulability (Thrombotest, TT) values and activities of clotting factors VII and X in breast fed infants at 2 weeks, 1 month, and 3 months of age after either oral or intramuscular vitamin K prophylaxis at birth Values are expressed as a percentage of normal adult pooled plasma.

Vitamin K_1 was extracted from 1 ml serum samples by a two step high performance liquid chromatographic (HPLC) procedure, according to the method of Lamber *et al.*[12 13] A few modifications were applied. The assays were performed with two Spectra Physics SP8800 systems equipped with Rheodyne 7125 manual injectors, with 100 µl sample loops. Vitamin $K_{1(25)}$ was used as an internal standard. The first HPLC step was used for preseparation of vitamin K_1 and $K_{1(25)}$ on a microspher-Si column (Chrompack). Locations of vitamin K_1 and internal standard were detected with a variable wavelength detector model 770 (Spectra Physics) set at 248 nm. Final separation and quantification were performed during the second HPLC step, using a microspher-C18 column (Chrompack) and postcolumn chemical reduction with tetramethylammonium-octahydridotriborate for fluorescence detection (λ_{ex}=325 nm, λ_{em}=450 nm) with a Waters 470 fluorescence detector (Waters, Millipore). Concentrations were calculated from relative peakheights of vitamin K_1 versus known amount of internal standard. Recovery of vitamin K_1 from standard solutions added to normal serum was 85±5%, with a detection limit of 45 pg/ml.

In all PIVKA-II positive samples and in about 30% of other samples alanine aminotransferase was determined (normal <40 U/l).

For statistical calculations χ^2, Student's *t*, Mann-Whitney U, and Wilcoxon's one sample tests and Spearman's rank correlation coefficient were used where appropriate.

The study was approved by the local medical ethical committee.

Results

None of the infants had clinical symptoms of bleeding diathesis or severely disturbed coagulation parameters.

The decrease in number of infants studied during follow up is caused by frequent stopping of exclusive breast feeding before the age of 3 months. Some values are missing due to sampling errors. The number of samples studied is stated where different.

Results of coagulation tests are shown in fig 1. Blood coagulability and activities of clotting factors VII and X revealed no difference between the two groups at any of the ages (Mann-Whitney, $p>0·05$). As is to be expected, a rise in activity between 14 and 30 days of age was found for these coagulation parameters (Wilcoxon, $p<0·01$).

Results of PIVKA-II determination are represented in table 2. Two weeks after birth PIVKA-II could not be demonstrated in any of the 285 infants studied. At 1 month PIVKA-II was detectable in four out of 262 infants: one in

Table 2 Presence of PIVKA-II (≥0·10 AU/ml) in breast fed infants of different ages after either oral or intramuscular vitamin K prophylaxis at birth

	Time after birth		
	2 weeks	1 month	3 months
Oral group	0 (n=145)	3 (n=135)	7 (n=68)
Intramuscular group	0 (n=140)	1 (n=127)	8 (n=63)

the intramuscular group (0·8%) and three in the oral group (2·2%). PIVKA-II concentrations ranged from 0·10 to 0·47 AU/ml. The difference in percentages of positive samples after oral compared with intramuscular administration is not statistically significant (χ^2, p=0·34). The 95% confidence intervals of the difference were −1·5 to 4·3%. At 3 months of age PIVKA-II could be detected in 15 out of 131 infants: seven in the oral group (10·3%) and eight in the intramuscular group (12·7%). The 95% confidence interval of the difference between the oral and intramuscular group was −13·3 to 8·5% (p=0·67). PIVKA-II concentrations ranged from 0·10 to 0·32 AU/ml.

Vitamin K_1 plasma concentrations decreased significantly during follow up in both groups (Wilcoxon, p<0·001); fig 2). At 2 weeks of age the mean (SD) concentration of 1608 (873) pg/ml in the intramuscular group (n=64) was significantly higher than that of 815 (414) pg/ml in the oral group (n=74) (Mann-Whitney, p<0·0001). At 1 month of age the concentration was still significantly higher in the former group: 615 (272) pg/ml (n=84) *v* 391 (207) pg/ml (n=94); p<0·0001. Remarkably, at 3 months of age concentrations were still slightly different: 329 (186) pg/ml (n=57) *v* 268 (174) pg/ml (n=62); p=0·03. Plasma concentrations of vitamin K_1 did not correlate with sex, gestational age, birth weight, Apgar score, or arterial cord blood pH, nor with blood coagulability, activities of factor VII or X, or PIVKA-II concentration.

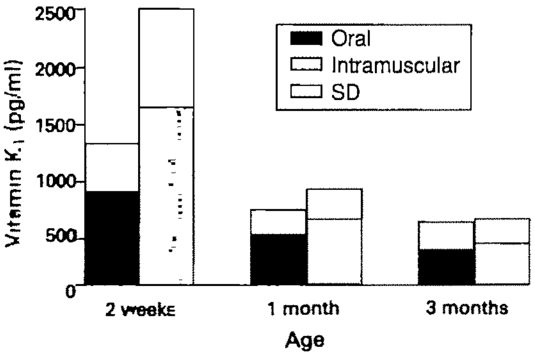

Figure 2 Mean (SD) vitamin K_1 plasma concentrations in breast fed infants at 2 weeks, 1 month, and 3 months of age after either oral or intramuscular vitamin K prophylaxis at birth.

In table 3 individual results of PIVKA-II, blood coagulability, factors VII and X, vitamin K_1, and alanine aminotransferase determinations are shown for the infants positive for PIVKA-II. Values for blood coagulability and factors VII and X were not different from infants negative for PIVKA-II. Similarly, vitamin K_1 concentrations were not extremely low. At 3 months of age mean (SD) vitamin K_1 concentration in the infants positive for PIVKA-II was 221 (74) pg/ml compared with 312 (191) pg/ml in the infants negative for PIVKA-II (Mann-Whitney, p=0·16). Results of the alanine aminotransferase determinations indicate that liver dysfunction is not a major cause for the appearance of PIVKA-II. No relevant correlations between the concentration of PIVKA-II and other parameters could be detected.

Discussion

Concentrations of vitamin K_1 in blood vary widely, according to the diet of the subject and the method used. The reference range reported for fasting adults, measured by a technique comparable with ours, ranges from 62–980 pg/ml.[14] The reference range for neonates and infants is still unknown. Mean plasma concentrations in healthy breast fed infants of 1 month of age without vitamin K prophylaxis are reported to be 500–700 pg/ml.[10 15] Formula fed infants have much higher concentrations of

Table 3 Results of PIVKA-II, blood coagulability clotting factors VII and X, vitamin K_1 and alanine aminotransferase in PIVKA-II positive infants

Group	Age (months)	PIVKA-II (AU/ml)	Blood coagulability* (%)	Factor VII* (%)	Factor X* (%)	Vitamin K_1 (pg/ml)	Alanine aminotransferase† (U/l)
Oral	1	0·47	90	44	57	‡	21
Oral	1	0·16	70§	77	47	189	15
Oral	1	0·12	>100	60	43	243	6
IM	1	0·10	>100	74	51	436	23
IM	3	0·32	>100	99	52	190	20
IM	3	0·31	100	85	61	220	58
IM	3	0·29	>100	61	52	238	31
Oral	3	0·28	>100	70	47	140	16
Oral	3	0·22	>100	66	51	125	13
IM	3	0·19	>100	95	74	328	17
IM	3	0·14	65§	78	48	357	26
IM	3	0·14	>100	62	54	235	8
Oral	3	0·13	70§	74	48	126	20
Oral	3	0·12	57§	66	49	263	12
IM	3	0·11	>100	89	43	242	44
IM	3	0·11	>100	72	67	‡	16
Oral	3	0·11	>100	89	46	184	11
Oral	3	0·10	>100	67	63	357	18
Oral	3	0·10	—	64	37	‡	19

*Blood coagulability and factors VII and X are expressed as a percentage of normal adult pooled plasma.
†Alanine aminotransferase: normal value<40 U/l.
‡Missing value due to insufficient volume of serum
§Activity less than mean −2 SD of PIVKA-II negative infants of that age.
IM=intramuscular

3000–4500 pg/ml, because of the relatively high concentration of vitamin K_1 in formula (60 μg/l) compared with human milk (2 μg/l).[10 15] McNinch *et al* reported vitamin K_1 plasma concentrations in breast fed infants after 1 mg vitamin K_1 orally or intramuscularly at birth.[4] In the oral group the peak median concentration occurred earlier, but was lower. In both groups vitamin K_1 concentrations declined rapidly, after 24 hours the mean was 23 ng/ml in the oral group and 444 ng/ml in the intramuscular group. The present study demonstrates that at 2 weeks of age vitamin K_1 concentrations are still raised; concentrations of about 1600 pg/ml after intramuscular injection and of 800 pg/ml after oral administration were found. At 1 month of age concentrations declined to about 600 and 400 pg/ml, respectively. Other reports confirm that four to six weeks after an intramuscular injection of 1 mg vitamin K_1, plasma concentrations are back at unsupplemented values.[10 16] Nevertheless, at all ages vitamin K_1 concentrations were lower after oral administration. To our knowledge, vitamin K_1 concentrations beyond the first week of life after a single oral dose were not reported before. To determine whether the lower vitamin K_1 plasma concentration after oral administration also entails a worse protection against vitamin K deficiency, we have to compare coagulation parameters.

Blood coagulability and activities of clotting factors VII and X showed no difference between the two groups. However, these coagulation tests are not sensitive enough to detect biochemical vitamin K deficiency.[17] Accordingly, blood coagulability and factors VII and X were not different in PIVKA-II positive infants compared with those who were PIVKA-II negative. In contrast to vitamin K_1 plasma concentrations and activities of clotting factors, PIVKA-II detection is a more direct reflection of vitamin K dependent carboxylation of clotting factors in the liver. As mentioned previously, detection of PIVKA-II has no clinical consequences, but it does indicate whether enough vitamin K has been available to carboxylate all vitamin K dependent proteins. Prolongation of low vitamin K intake may lead to serious complications.

In cord blood, using the same method as we did, Motohara *et al* detected PIVKA-II in 21·5% of 102 samples.[18] At 3 to 5 days of age 50 to 60% of infants were PIVKA-II positive if they were breast fed and had not received vitamin K prophylaxis at birth.[18] At the age of 1 month 12·3% were positive.[19] Biochemical vitamin K deficiency occurs frequently in unsupplemented breast fed infants. Widdershoven *et al* compared PIVKA-II concentrations in breast fed and formula fed infants.[10] At 4 days of age about 10% of both groups had PIVKA-II in their blood. At 1 month of age PIVKA-II was not detected in any formula fed infant, compared with in 5·5% of breast fed infants. At 3 months of age no formula fed infant was positive, compared with 7·5% of breast fed infants. Thus, formula feeding seems an effective way to prevent the appearance of PIVKA-II in the blood of young infants, probably due to the high intake of vitamin K_1.

PIVKA-II was not detectable in any of our infants at 2 weeks of age. This corresponds with the raised vitamin K_1 concentrations in both groups. Surprisingly, in four 1 month old infants PIVKA-II was detected. However, the concentration in the only positive infant of the intramuscular group was at the limit of detection. So, in the intramuscular group hardly any 1 month old infant had PIVKA-II detectable, while it was detectable in a few in the oral group. Exact comparison of our PIVKA-II results with those of Motohara *et al*[10] and Widdershoven *et al*[10] is hampered by the fact that our method is more sensitive. Their detection limit amounted to 0·13 compared with 0·10 AU/ml in our study. If we applied their detection limit as a selection criterium just two 1 month old infants would remain positive, thus strengthening the clinically relevant difference in PIVKA-II detectability between our supplemented and their unsupplemented 1 month old breast fed infants (χ^2, $p<0{\cdot}01$). Even without correction, PIVKA-II was less frequently detected in our intramuscular group than in the unsupplemented infants of Widdershoven *et al* (1/127 *v* 4/73, $p<0{\cdot}05$).[10] Our oral group did not differ significantly from the unsupplemented infants of Widdershoven *et al* (3/135 *v* 4/73, $p=0{\cdot}21$). This demonstrates that intramuscular vitamin K seems still effective at the age of 1 month, while oral vitamin K is not.

Surprisingly, at the age of 3 months a high percentage of children in both our oral and intramuscular groups had PIVKA-II detectable, indicating that neither route was completely effective by that age. Vitamin K_1 concentrations declined to values of 300 pg/ml. Although vitamin K_1 concentrations in the intramuscular group were slightly higher than in the oral group, both concentrations seem insufficient to prevent biochemical evidence of vitamin K deficiency in all infants. Other reports confirm the reappearance of PIVKA-II after a single vitamin K administration at birth. Motohara *et al* reported a decrease in PIVKA-II detectability on the third and fifth day of life after a single oral dose of 5 mg vitamin K_2 at birth.[18] At 1 month of age, however, no significant reduction in PIVKA-II detectability was demonstrated unless a second oral dose was administered at 14 days of age.[19] Widdershoven *et al* detected PIVKA-II in none of 48 infants of 1 month old, in one of 29 infants of 2 months old, and in one of 23 infants of 3 months old after the administration of 1 mg vitamin K_1 intramuscularly at birth.[10]

We failed to detect an association between PIVKA-II and vitamin K_1 plasma concentrations. Vitamin K_1 concentrations were not different in PIVKA-II positive children compared with PIVKA-II negative infants. This may be caused by the fact that PIVKA-II has a half life of about 70 hours and hence can still be present in plasma even when the vitamin K deficiency has been corrected.[9] Moreover, due to frequent feeds, plasma concentrations of vitamin K_1 in infants vary widely. The plasma half life of tritiated vitamin K_1 has been reported to be 120–150 minutes.[20] Information about hepatic vitamin K stores in infants is limited. Shearer *et al* reported that in unsupplemented term neonates hepatic vitamin K_1 concentrations were no more than about 1 ng/g liver (fresh weight).[21] Total liver stores amounted to 0·1 μg. In adults a much higher mean concentration of 5·5 ng/g was measured, resulting in total stores of 8 μg. When the newborn had been given an intramuscular injection of vitamin K_1 (0·5–1·0 mg) endogenous hepatic values remained raised for at least one week. Besides vitamin K_1 different forms of vitamin K_2 (menaquinones 6 to 12) could be detected in the liver.[21] In adults menaquinones even accounted for some 75–97% of total hepatic stores of vitamin K on a molar basis. In the neonate, however, menaquinones were not detectable until about 14 days postpartum. Thereafter a gradual build up was indicated and adult concentrations were attained about one month after birth.[21] However, the extent of vitamin K_2 utilisation remains controversial. Nevertheless, besides vitamin K_1 vitamin K_2 has to be considered when assessing vitamin K status. Altogether, the plasma vitamin K_1 concentration may not adequately represent the total amount of vitamin K that is available as a cofactor for the carboxylase enzyme in the liver.

Wallin has reported evidence to maturation of the vitamin K dependent carboxylation system in fetal-neonatal rats.[22] At 7 days of neonatal age adult values of carboxylase activity were reached. But activities of the two pathways that provide carboxylase with reduced vitamin KH_2 cofactor (vitamin K epoxide reductase and vitamin K reductase) were never as high as in adult liver. In other words, it might be possible that an increased requirement of vitamin K exists in early infancy, due to immature reutilisation of vitamin K epoxide. The vitamin K_1 reference range for fasting adults can not be applied automatically to non-fasting young infants. Moreover, individual difference in enzyme maturation and therefore individual difference in vitamin K requirement could exist.

To summarise, single oral or intramuscular administration of 1 mg vitamin K_1 postnatally may not offer complete protection against late biochemical vitamin K deficiency. Correspondingly, except for one infant with classical haemorrhagic disease of the newborn,[23] most case reports of failures of vitamin K prophylaxis concern late disease.[1 24] Epidemiologically, intramuscular vitamin K prophylaxis appears to have a lower incidence of failure.[6–8] In a recent survey in the British Isles, 27 cases of haemorrhagic disease of the newborn were recorded.[8] Seven of them occurred in spite of oral vitamin K prophylaxis at birth. No failures were recorded after intramuscular administration, although there was uncertainty about intramuscular vitamin K in one case. The relative risk for babies who had received oral vitamin K compared with babies who had received intramuscular vitamin K was 13:1. The relative risk without prophylaxis was 81:1.[8] A schedule of repeated oral doses was considered.[25] Taking our results as well as epidemiological evidence into account, we suggest that for complete protection of breast fed infants against late haemorrhagic disease of the newborn, vitamin K administration should be repeated. Whether a monthly, weekly, or daily administered oral dose should be recommended deserves further investigation.

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Oscillations of body temperature at night

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Abstract

There is increasing evidence that overheating is a contributing factor for some cot deaths. One hypothesis is that infant thermoregulation is closely related to respiratory control. To test this hypothesis it was necessary to determine the normal pattern of body temperature in the developing infant. A system has been designed and built to record continuously temperature signals from ambient, rectal, and various skin site sensors. Overnight studies were performed on 30 infants aged between 2 and 26 weeks in a hospital ward.

Various time and frequency domain analyses of the temperature data have been developed. Analysis of body temperature rhythms has confirmed patterns during sleep which mature with age. In addition a periodic oscillation of body temperature has been found with a cycle of approximately one hour. This oscillation may reflect sleep state and its further study may give an insight into control of infant thermoregulation and the integration of this control with that of breathing and the cardiovascular system.

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There is abundant evidence that there is a relation between cot death and temperature. Cot deaths occur more often in winter than in summer,[1–4] more in higher latitudes in temperate zones,[5] and overheating may be a contributing factor in many deaths.[6–8] The physiological processes linking temperature changes to cot death have not been established.

Our hypothesis is that an increased body temperature, or thermal stress, is associated with increased respiratory instability. To test this hypothesis we first needed to determine the normal pattern of body temperature in the developing infant.

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Subjects and methods

Our continuous temperature measurement studies were carried out in a hospital ward using a dedicated computer based polygraphic recording system (BabyLog).[9] The ambient temperature of the hospital ward was 23–25°C throughout these studies, and all infants were lightly clothed in the equivalent of a cotton vest and a nappy. Infants were enrolled if they were considered afebrile by their doctor, did not have an infectious or inflammatory illness, and had no known encephalopathy. Recordings were completed on 30 such infants who had presented with minor choking episodes for which there was no obvious cause found on polysomnographic study. Their ages ranged from 2 to 26 weeks. Ethics committee approval and written parental informed consent were obtained for these studies.

The infants had continuous recordings of ambient and various body temperatures overnight for at least 12 hours. Rectal temperature was measured 5 cm from the anal margin and skin temperature from the forehead, axilla, wrist, abdomen, shin, and foot. We used temperature sensors which are based on a semiconductor rather than a thermistor. We have previously described the design, manufacture, and testing of these sensors, and the interface with our polygraphic recording system though a multiplexing isolating amplifier.[10] The multiple temperature channels were sampled once a second and the signal data were stored on the computer system for later analysis. Sleep state, feeds, nappy changes, and other behaviour were recorded on a diary sheet and by continuous video monitoring.

Software has been written to produce a graphical output of the signal data and to allow measurement of any temperature recording at any sample point. Algorithms have also been developed for spectral analysis.[11] These software algorithms process the temperature data in the Fourier domain to produce a screen output with peaks corresponding to dominant oscillations. The frequency, and hence period, of each of these peaks is determined on screen. The largest peak corresponds to the dominant frequency for a particular recording.

The temperature signals were than examined using the graphical software we have written for our system. Oscillations which varied in amplitude by more than 0·1°C were measured for the length of period from peak to peak. These measurements of each identifiable period were then averaged (with 95% confidence intervals) for each recording.

Results

Thirty overnight studies have been examined in detail. Figure 1 presents an example of an overnight rectal temperature recording. Graphs of the continuous recordings showed trends on visual inspection that have been confirmed by further analysis.

SLEEP-WAKE PATTERNS

The variation in rectal temperature over a single night was 0·4–0·7°C in the younger infants (less than 8 weeks old) but was as much as 1·5°C in

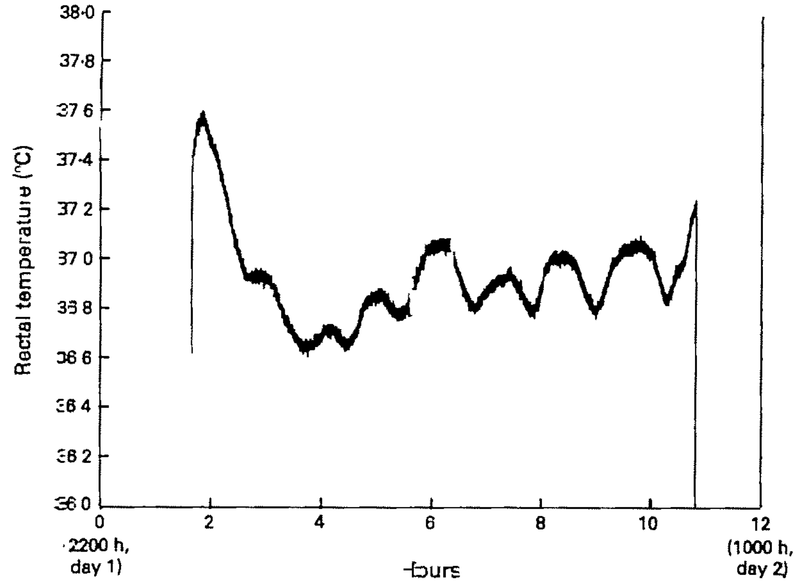

Figure 1 Continuous recording of rectal temperature in a 6 week old infant Time in hours (from 2200 h) on the x axis and temperature (°C) on the y axis. Data were obtained once a second from bedtime until she was lifted from her cot in the morning. The graph shows the initial decrease in temperature, interrupted by a 'shoulder', then oscillations throughout the night with a cycle of approximately one hour.

those more than 12 weeks old. In an individual recording the temperature commonly varied from 37·8 to 36·3°C through the night. When an infant went to sleep the rectal temperature decreased over about an hour to a nadir, then slowly increased until the infant woke for a feed or nappy change, when the temperature increased more quickly, and remained at this level until the infant went to sleep again. The decrease in temperature when sleeping after such a feed or nappy change was not as sudden as that seen on first going to sleep.

In infants under 4 weeks of age the axillary temperature reflected the rectal temperature fairly well, but in the older infants there was little similarity between axillary and rectal temperatures. The wrist, shin, and foot temperatures showed opposite trends to the rectal temperature with a rapid increase of several degrees over about the first hour after falling asleep, and a rapid decrease when waking for a feed or nappy change. The forehead temperature followed neither the rectal nor the 'peripheral' pattern.

The extent and duration of this decrease in rectal temperature on first going to sleep was examined in relation to age for each infant (fig 2). The decrease was seen in the 26 infants older than 4 weeks but not in the four infants less than 4 weeks old. There was a tendency for the temperature to decrease more in older infants. There was little correlation of age with the duration of the decrease, which could take anything from 30 to 120 minutes (fig 2B; *r*=0·40).

RECTAL TEMPERATURE OSCILLATIONS

In addition to the sleep-wake patterns described, we found a small amplitude oscillation of rectal temperature in 24 of the 30 continuous recordings. The amplitude of this oscillation was between 0·2 and 0·3°C. The frequency of the oscillation was determined by two methods.

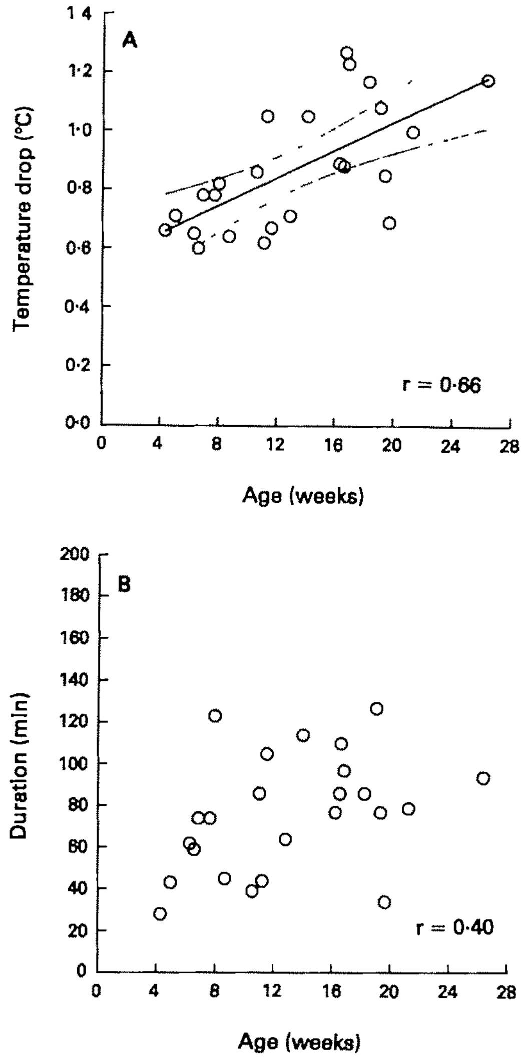

Figure 2 Characteristics of the decrease in rectal temperature after bedtime. (A) Degree of the decrease related to age for each infant. A linear regression (with 95% confidence intervals) is fitted and has a coefficient of 0·66, showing a trend to a greater decrease in older infants. (B) Duration of the decrease in temperature showing a poor correlation with age and a wide scatter lasting from 30 up to 120 minutes in different infants.

Spectral analysis was used to determine the dominant frequencies of any and all oscillations of the rectal temperature during the entire night of each recording. In six of 30 recordings no obvious spectral periods were identified. These six recordings were from infants less than 5 weeks old. In those infants more than 5 weeks old a sleep-wake cycle of three to four hours was identified and, in addition, spectral periods were found with a cycle length of approximately one hour. Figure 3A presents these spectral periods in relation to age for each infant, showing the cluster around a one hour cycle length.

To define these oscillations more accurately, the raw signals from each rectal temperature recording were examined using computer software graphical methods. All distinct oscillations that could be identified (see fig 1) were measured. In six recordings distinct oscillations could not be found (the same six infants in whom spectral analysis did not identify obvious periods). In the 24 recordings from infants more than 5 weeks old the number of distinct

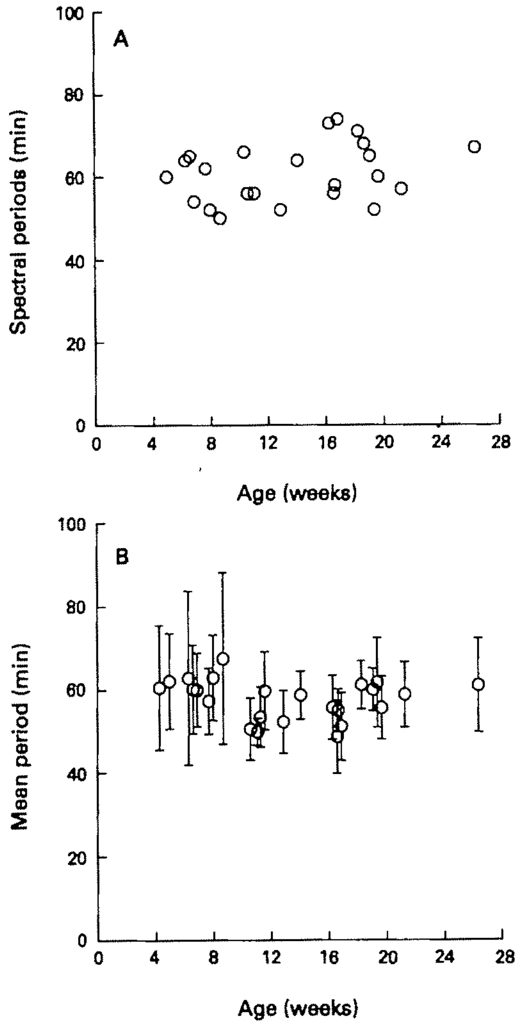

Figure 3 Two methods of determining the cycle length of the short term oscillations of rectal temperature related to the age of each infant. (A) Period of the frequencies detected by spectral analysis of each of the overnight recordings from bedtime until morning. (B) Mean period and 95% confidence intervals of individual oscillations detected in each infant's recording. The two methods illustrate the approximately one hour cycle of these temperature oscillations.

oscillations varied between four and 12. The duration, or period, of each oscillation was measured and the mean period (95% confidence intervals) of the oscillations for each infant was calculated. Figure 3B presents these mean periods in relation to the age of each infant and shows the means clustered closely around one hour. The overall mean of the periods of the combined 24 studies was 58 (confidence interval 2·1) minutes.

Discussion

Our hypothesis is that an infant's control of breathing is linked to temperature. To test this hypothesis we first needed to determine the normal pattern of body temperature in infants. As we are particularly interested in vulnerability to cot death, we focused on physiology during sleep in the developing infant during the first months of life.

Studies were undertaken in a hospital environment with a controlled ambient temperature and similar clothing insulation for all infants. These studies have shown certain patterns of body temperature and also proved that there is no reasonable alternative to measuring rectal temperature for continuous recording. A number of different skin sensors were used, including axilla, abdomen, forehead, wrist, shin, and foot, and none was found to correlate well with the rectal probe.[10] Consideration was given to other methods of body temperature measurement such as tympanic membrane sensors or remote detection of microwaves. Techniques applicable in a hospital or laboratory environment are, however, unsuitable for long term use in a sleeping infant who is not under constant surveillance. We plan to extend our studies to the home environment and the requirements of reliability, durability, safety, and ease of use for parents guided our selection of equipment and techniques.

To determine patterns of body temperature accurately it is essential to measure continuously rather than take a few intermittent recordings. We chose to sample once a second, although once per minute would suffice. This sampling rate can produce much redundant data, but provides the facility to then use averaging algorithms or to search for frequencies of any period with spectral analysis without being limited by the basic sampling frequency. We report oscillations with a period of approximately one hour, but are able to identify other periodic changes (so called biological noise) with much higher frequencies.

This continuous sampling procedure and use of the entire data sets in analysis has uncovered short term oscillations of rectal temperature with a period of about 60 minutes. Other workers have also measured overnight rectal temperatures in infants and shown the initial decrease on going to sleep.[12 13] They did not observe the hourly oscillations seen in our studies, however, probably because of the method with which they produced their data sets. Although their temperatures were logged once a minute, for analysis purposes they used temperatures only every 15 or 30 minutes. The data set becomes much easier to handle, but with effective sampling at this frequency it would not be possible reliably to detect oscillations with a period of an hour or less.

We have confirmed several of the findings of these workers. The initial decrease in rectal temperature on going to sleep is a significant feature (fig 1 and 2). It appears in infants older than 4 weeks and its amplitude seems to increase in older infants, being as much as 1·3°C in those over 16 weeks. The duration of the decrease is not related to age and it is variable from less than 30 minutes to more than two hours. This variability in duration would be missed by sampling only every 15 or 30 minutes. The decrease itself is sometimes smooth to the nadir, but in some recordings is interrupted by a small 'shoulder' or rise, which appears to have the same amplitude and periodicity as the short term oscillations we have discovered.

Wailoo and coworkers took an arbitrary zero time for their analysis as the time of placing the infant in the cot, which ignores possible effects of any circadian rhythm due to the time of day but allows the determination of a pattern which seemed 'phase locked' to bedtime.[12 13] Our studies have confirmed that the temperature decrease on sleeping seemed obligatory and independent of bedtime.

Two different methods of analysis of our study data indicate that there is an oscillation of rectal temperature with a period of approximately one hour (fig 3). The cause and significance of these short term oscillations is intriguing. They seem to become apparent after the first month of life, at the same age as the appearance of sleep-wake patterns described as 'mature', with a definite initial decrease in temperature 'phase locked' to bedtime.[12 13]

Sleep state changes with a cycle of approximately one hour have been described in a 2 month old infant with alterations in the variability of heart rate and respiratory rate coincident with electroencephalogram and electromyogram changes.[14] Regularity in sleep alternation in a 3 month old infant has been shown with a cycle of about one hour.[15] This age is a time of maximum concordance between physiological variables, higher than at any earlier or later age. Electroencephalogram parameters develop a rhythmicity with approximately a one hour cycle after the first week of life and coupling of this rhythmicity with other physiological variables (respiratory and cardiac) begins to emerge at 3 to 4 months of age.[16] The hourly cycle of rectal temperature oscillations is therefore likely to be related to these sleep state changes, showing similar development with age. It may reflect phases of active sleep and indicate an increase in metabolic rate.

We plan to extend our studies to the home environment,[11] to examine respiratory and cardiac signals to define sleep states,[14] and any link between control of breathing and temperature. Analysis of these home recordings may allow us to determine the effects of thermal stress, both exogenous (ambient temperature, clothing, and bedding insulation) and endogenous (immunisations and infections), and to find any developmental changes in the individual infant over the first few months of life.

CONCLUSION

We have developed a computer based polygraphic recording system and modified it for future use in the home environment. Sampling at a high frequency has allowed analysis of continuous body temperature recordings. The rectal temperature rhythms of infants in the first six months of life show a previously unreported oscillation with a cycle of approximately one hour. This becomes apparent at around the same age as the maturation of a recently described pattern of rapid decrease in temperature after bedtime.

With the addition of respiratory and cardiac signal recordings we plan to investigate these oscillations and other rhythms to determine their relation with behavioural or sleep state and the effects of changes in age, ambient temperature, clothing, and bedding, immunisations and illness. We may also be able to examine the integration of control of thermoregulation with that of breathing and the cardiovascular system, particularly during sleep at the most vulnerable age for cot death.

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Factors affecting the development of night time temperature rhythms

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Abstract

The rectal temperature of 26 infants between 6 and 16 weeks old was monitored continuously for one night each week. Rectal temperature always decreased with sleep but the minimum temperature attained changed with age. Some time between 8 and 16 weeks old the minimum sleeping rectal temperature decreased abruptly from around 36·8°C to around 36·4°C. This change was complete within one week and did not normally revert unless the infant became ill.

Some infants changed as early as 8 weeks old, others not until 16 weeks. Breast fed infants changed significantly earlier than bottle fed infants. Girls changed significantly earlier than boys. First born infants changed significantly earlier than second or subsequent infants. Early changers were significantly more likely to be sleeping lateral or supine, and to have older mothers. They tended to come from more affluent families. There was no association between the time of change and the thermal environment in which the infant slept or the number of episodes of minor illness in the early weeks of life.

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When infants are first brought home their body temperature changes little over the course of the light-dark cycle and for the first weeks of life their rectal temperature decreases to about 36·8°C with sleep, whether this occurs by day or by night. In a previous cross sectional study[1] we showed that at around 10–12 weeks of age rectal temperature begins to decrease further with sleep at night than during the day, a night time pattern which persists into adulthood. Within two hours of bedtime rectal temperature decreases to less than 36·5°C and then remains low for a few hours before a gradual warming to around 37°C before waking.[2]

There appeared, however, to be considerable individual differences in the age at which this pattern appeared. This paper reports longitudinal studies of individual infants which confirm these differences, and shows some factors affecting the timing of development of night time temperature rhythms.

Subjects and methods

Thirty normal healthy full term infants were recruited at or just after birth by liaison with general practitioners and health visitors in Leicestershire. Parents gave informed consent to weekly overnight recordings of body temperature from 6 to 16 weeks of age. Basic perinatal data were collected at the time of recruitment and parents were provided with a diary to record prospectively any episodes of illness in the infant.

Once each week from 6 weeks' old the infant was visited at home in the evening, weighed naked, and data collected on the current feeding regimen, other aspects of parental care, and the health of the infant and family. Probes were then attached to record body temperature. A soft probe, inserted 5 cm from the anal margin, recorded rectal temperature and a skin thermistor measured surface temperature on the skin. Only rectal temperature data are described here. A third probe measured ambient temperature near the infant. All three probes were connected to a Grant Squirrell data logger, set to sample at one minute intervals throughout the night. These techniques are safe,[1] and full ethical approval was obtained for the study.

Parents were asked to keep a detailed diary of all events throughout each night of recording, including feeds, nappy changes, periods of waking, and administration of any drugs. Note was also made of infant's clothing and bedding so that a thermal insulation or 'tog' value could be calculated according to tables provided by the Shirley Institute (Manchester).

The next day the data loggers were collected and the data downloaded to a computer. They were analysed for technical problems such as loss of probes and only unblemished data were analysed further. For each night of recording rectal temperature was abstracted at 30 minute intervals from one hour before bedtime until nine hours later.

Results

Twenty six of the 30 subjects yielded sufficient data to be certain of the individual pattern of development, a total of 246 nights of recording. For the remaining four infants data were not available for one or more weeks around the critical age for a variety of reasons. The mean (SD) gestational age of the 26 infants was 39·9 (1·5) weeks, with all but one born between 38 and 42 weeks and none before 36 weeks. The birth weight averaged 3471 (485) g and 13 were boys. The average maternal age was 27·3 (4·6) years. Six of the infants had parents in occupational groups 1 or 2, and seven in groups 4 or 5, a social class distribution similar to that of the Leicestershire population as a whole. Nine were first children; three had two or more older siblings.

CHANGES IN SLEEPING RECTAL TEMPERATURE WITH AGE

At all ages studied rectal temperature decreased with sleep at night reaching a minimum between one and four hours after bedtime, as reported previously.[1 2] The minimum temperature attained by any infant, however, changed with age. Figure 1 shows a typical example of individual development. The minimum rectal temperature decreased suddenly by 0·3–0·5°C between one week and the next, though this occurred at different ages in different subjects. Figure 2 shows how the minimum rectal temperature changed with age in five further infants. All 26 infants studied showed similar abrupt changes in minimum rectal temperature. As in our previous studies there was no significant change in the thermal environment after 6 weeks of age.

Once this abrupt transition to a lower minimum night time rectal temperature had occurred, the minimum remained low unless the infant was incubating an illness. Figure 3 shows data from all subjects normalised to the first week in which rectal temperature decreased below 36·5°C, which we have called the 'adult' pattern.

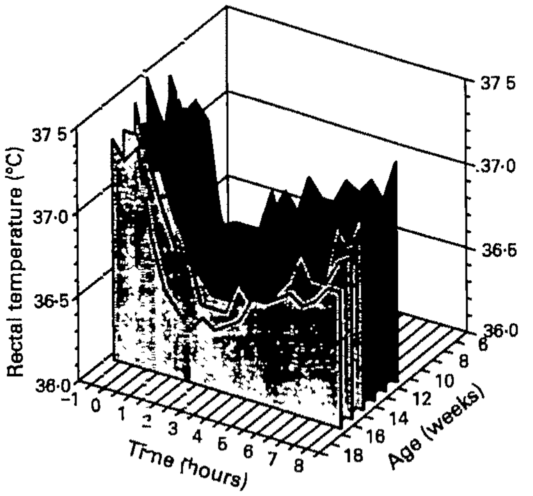

Figure 1 Pattern of rectal temperature change overnight at different ages in a typical infant.

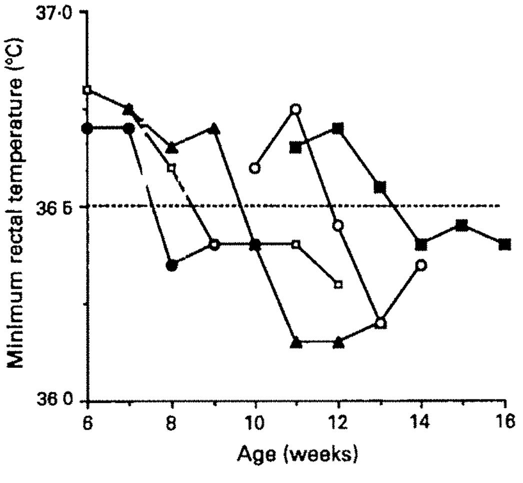

Figure 2 Minimum rectal temperature at night at various ages in five infants not including that illustrated in fig 1. The largest and smallest decreases in minimum rectal temperature between two weeks are illustrated.

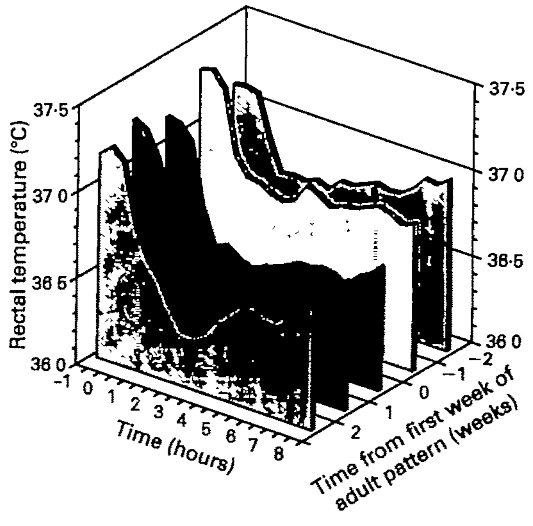

Figure 3 Averaged data from all 26 infants normalised to the first week in which minimum rectal temperature decreased to less than 36·5°C. Standard errors (range 0·03–0·08°C) are not shown for reasons of clarity.

There was a highly significant change in rectal temperature from the week before to the week in which temperature first decreased (p<0·01, Student's *t* test), but no significant differences between the weeks after or before the change. Excluding periods of known illness only one of the 26 infants had a minimum rectal temperature greater than 36·5°C again after the week in which it first decreased to less than 36·6°C. On a few occasions, however, infants showed higher minimum temperatures the night before an illness such as upper respiratory tract infection.

We therefore chose the age at which the minimum rectal temperature first decreased to less than 36·5°C as the age of 'maturation' of the night time temperature rhythm. The mean (SD) age was 11·1 (2·5) weeks. Twelve of the infants matured between 7 and 11 weeks old (inclusive) and 14 between 12 and 16 weeks.

FACTORS AFFECTING THE AGE OF 'MATURATION'

The infants who developed their mature temperature rhythms before 12 weeks old were significantly more likely to have been breast fed at birth (χ^2=5·26, p<0·025) and for at least six weeks (χ^2=5·56, p<0·025). The average chronological age of development of the rhythm for infants who were never breast fed was 12·38 (0·52) weeks, whereas those breast fed for at least six weeks developed at 10·07 (0·74) weeks, a significant difference (p<0·01, Student's *t* test). Girls developed their rhythms significantly earlier than boys (average age for girls 10·23 (0·59) weeks; for boys (11·92 (0·44) weeks; p<0·05, Student's *t* test). There was a clear relation between the weekly rate of weight gain and the age of 'maturation' of the rhythm. Infants gaining weight most rapidly developed later (product moment correlation between average weekly weight gain and age of development (*r*=0·513, p<0·01).

First children matured significantly earlier than second or subsequent children (average age for first children 10·11 (0·74) weeks; for second and subsequent children 12·58 (0·42) weeks;

$p<0{\cdot}05$, Student's *t* test). There was, however, no significant association between breast feeding and birth order. Infants sleeping prone were significantly more likely to develop their rhythms after 11 weeks old ($\chi^2=5{\cdot}51$; $p<0{\cdot}025$) though they were also significantly more likely to be second or subsequent children ($\chi^2=4{\cdot}34$; $p<0{\cdot}05$). The mothers of babies who matured before 12 weeks old were significantly older than those of babies who matured later ($p<0{\cdot}05$, Student's *t* test) and there was a strong trend, close to significance, for infants from families in the non-manual occupational groups to mature earlier than those from families in manual groups. There was no significant difference in room temperature or thermal insulation of clothing and wrapping between infants who developed before and after 11 weeks old. Infants who developed after 11 weeks old had not had more episodes of minor illness (such as upper respiratory tract infection) in the first weeks of life.

We have also analysed our data correcting for the small differences in gestational age between infants. All effects which were statistically significant with chronological ages remained significant when ages were corrected to a standard 40 week gestation.

Discussion

We have confirmed earlier observations that the minimum rectal temperature during sleep at night decreases abruptly around 11 weeks old.[2] The transition from a minimum sleeping rectal temperature around 36·8°C to a minimum around 36·4°C was rapid. It was always complete between two weeks' recordings, and the few more frequent recordings we have suggested a time course of two or three days. Once the change occurred it did not revert unless the infant was ill. We saw only one occasion where the minimum sleeping rectal temperature of a healthy infant returned above 36·5°C after the change.

As we have reported previously the change in sleeping temperature usually coincided with an abrupt lengthening of the time infants spent in their cots before disturbing their parents.[2] Not all infants, however, had settled into a regular sleep pattern at the time of 'maturation'. In particular, many breast fed infants were still feeding at night after the minimum rectal temperature decreased to less than 36·5°C.

The abruptness and permanence of the change suggests that it is a physiological alteration on the endogenous mechanisms of temperature control. Its timing seems to result from an interaction between features of the infant and the way in which it is cared for. This leads to large individual differenes in timing with some infants 'maturing' at twice the age of others. We have identified a series of factors associated with early and late development. They mostly relate to one another and it is impossible at this stage to say which are primary and which secondary associations.

Breast fed babies 'matured' significantly earlier than bottle fed babies. This occurred even if babies were breast fed for just one or two weeks, suggesting that it was due to having received breast milk, rather than the process of breast feeding, which may have stopped by the time maturation occurred. Breast milk contains a variety of substances which are absent from formula feeds and which might interact with central mechanisms of development. Melatonin is a possibility. Girls matured significantly earlier than boys, though they were more likely to be breast fed. In the first weeks of life boys gained weight faster than girls, especially if bottle fed. Late maturation of temperature rhythms was associated with high rates of weight gain. We do not know whether the boys gained weight more quickly and matured temperature rhythms later because of some physiological consequence of masculinity, or because they were treated differently by parents, being more likely to be changed to bottle feeding. The relation between sleeping position and the timing of development is fascinating but inexplicable.

The remaining factors which were associated with early or late maturation were all features of the infant's family environment. Second babies developed later. Babies with older mothers developed earlier. Perhaps some feature of the general household environment such as the amount of parental contact or sensory stimulation affects the processes of development.

It is clear, however, that the development of something as simple as the daily rhythm of body temperature is the result of a complex interaction between intrinsic and extrinsic factors which could in principle be changed by intervention should particular patterns of development be shown to affect morbidity or mortality.

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1 Wailoo MP, Petersen SA, Whittaker H, Goodenough P Sleeping body temperature in 3–4 month old infants. *Arch Dis Child* 1989,64:596–9
2 Lodemore MR, Petersen SA, Wailoo MP. The development of night time temperature rhythms over the six months of life. *Arch Dis Child* 1991,66:521–4.

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Paediatric cardiac transplantation with steroid-sparing maintenance immunosuppression

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Abstract

In order to determine the results of steroid-sparing maintenance immunosuppression in paediatric patients who have undergone orthotopic heart transplantation (OHT), a retrospective study was undertaken in 12 children and five infants (median age 3·5 years). Preoperative diagnoses were cardiomyopathy in seven and congenital heart disease in 10 patients. Immunosuppression was induced by cyclosporin, azathioprine, methylprednisolone, and antihuman lymphocyte immune globulin. It was maintained with cyclosporin and azathioprine. After induction, five patients received no further steroids. The remainder, except one, required only pulses for rejection (13 episodes or 0·51 episodes/patient year). Long term complications included hypertension in six, and renal impairment in three children. There were no early or late deaths from infection. Actuarial survival was 94% at one year. Of the children followed up for more than one year, all demonstrated an increase in height SD scores (mean (SD) −2·15 (1·35) to −1·15 (1·16)). We conclude that a steroid-sparing maintenance immunosuppression regimen can be successfully employed in paediatric OHT, and that significant catch-up growth can be achieved postoperatively.

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Cardiac transplantation is now an accepted form of treatment for infants and children with end stage cardiac disease. Since 1984 more than 1100 such procedures have been performed worldwide in children up to the age of 18 years, and cardiac transplantation in infants younger than 1 year old has been the most rapidly growing area during the last five years.[1] Actuarial survival of 72% at one year and 60% at five years is being achieved internationally.[2] The improved survival of cardiac transplant recipients with cyclosporin based immunosuppression is well established, but controversy remains as to whether steroids should be used in the paediatric patient, particularly in view of its long term side effects in this age group.[2] [3] Since the inception of our paediatric cardiac transplant programme in 1987, we have adopted a steroid-sparing regimen for maintenance immunosuppression. This report summarises our experience in 17 children under the age of 13 years who have received an orthotopic heart transplant (OHT).

Table 1 Details of paediatric cardiac transplant recipients

Case No	*Diagnosis*	*Previous surgery*	*Age*	*PVRI*	*Donor recipient*[1]	*Inotropes*
1	Cardiomyopathy	—	5 months	3·6	1·3	Yes, ventilated
2	CHD	Yes	2·4 years	—	1·3	No
3	Cardiomyopathy	—	8 years	6·7	1·3	No
4	CHD	Yes	8·1 years	1·4	1·5	No
5	Cardiomyopathy	—	12·2 years	<1	0·9	No
6	CHD	Yes	11 years	3·0	1·4	No
7	Cardiomyopathy	—	9·7 years	4·8	1·1	Yes
8	CHD	No	5 weeks	—	—	Yes, ventilated
9	CHD	Yes	4·8 years	5·0	2·2	No
10	CHD	Yes	3 years	—	1·9	No
11	CHD	Yes	3·5 years	2·1	1·6	No
12	CHD	No	3 years	4·5	1·7	No
13	CHD	Yes	8 years	1·6	1·2	No
14	Cardiomyopathy	—	5·4 months	3·0	2·1	Yes
15	Cardiomyopathy	—	9·2 months	—	1·1	Yes
16	Cardiomyopathy	—	10 weeks	—	1·8	Yes, ventilated
17	CHD	No	3·7 years	—	1·1	No

CHD=congenital heart disease, PVRI=pulmonary vascular resistance index
[1] Donor recipient weight ratio

Patients and methods

Between October 1987 and August 1991, 17 OHTs have been performed in 17 children at the Freeman Hospital, Newcastle upon Tyne. The patients ranged in age from 5 weeks to 12·2 years (median 3·5 years), with five infants under the age of 1 year. Patient details are illustrated in table 1. The preoperative diagnoses were cardiomyopathy in seven children and congenital heart disease in 10. Of the latter, seven had previously had closed heart surgery: four had pulmonary artery banding and three had systemic to pulmonary arterial shunts. Six children were in hospital and dependent on inotropes, and three were ventilator dependent before OHT. Sixteen of the 17 children survived OHT and have been followed up from 38 days to 3·8 years (median 1·4 years). The case records of these children were reviewed to determine the incidence of rejection, hospital admissions for intercurrent illnesses, and late complications. Growth data was available from standing height measurements in 11 children who had been followed up for more than one year. For comparative purposes, height and velocity were expressed as SD scores.[4] Renal function was assessed by a calculated glomerular filtration rate (GFR) based on Barratt's formula.[5] This formula is only applicable to children older than 6 months: a figure of >80 ml/min/1·73 m^2 was taken to indicate normal GFR.

IMMUNOSUPPRESSION

Immunosuppression was induced by the oral administration of cyclosporin 10 mg/kg and intravenous administration of azathioprine 4 mg/kg two hours before OHT. Peroperatively, methylprednisolone 10 mg/kg was given intravenously at the end of cardiopulmonary bypass, and three further doses of 2 mg/kg were given at eight hourly intervals in the first 24 hours. The postoperative immunosuppression regimen consisted of oral cyclosporin (8 mg/kg/day), oral azathioprine (1–3 mg/kg/day), and intravenous antilymphocyte globulin (Lymphoglobulin, Institut Mérieux, 5 ml/10 kg/day) for the first seven days. Cyclosporin dosage was adjusted to maintain a trough concentration of 400 ng/ml (radioimmunoassay for whole blood, Incstal Ltd) for the first six weeks, reducing to 200 ng/ml thereafter. Azathioprine dosage was adjusted to maintain the white cell count greater than 4×10^9/l. Steroids were not used for maintenance immunosuppression. Prophylactic flucloxacillin was given in the early postoperative period. Broad spectrum antibiotic cover was avoided for prophylaxis or treatment. Sulphamethoxazole–trimethoprim (three days per week), acyclovir, and nystatin were administered orally for 12 weeks as prophylaxis against *Pneumocystis carinii*, herpes simplex, and candida respectively.

REJECTION SURVEILLANCE AND TREATMENT

Non-invasive rejection surveillance via cross sectional and M mode echocardiography was the norm, supplemented by endomyocardial biopsy in suspicious cases in children older than 1 year. Echocardiography was performed twice weekly for six weeks, at weekly intervals thereafter until 12 weeks, fortnightly intervals thereafter until six months, monthly intervals thereafter until 1 year, and then every six weeks indefinitely, or as clinically indicated. A reduction in fractional shortening, an increase in left ventricular wall thickness, or the detection of a new pericardial effusion were taken as signs of rejection. Rejection was diagnosed whenever these signs were associated with clinical features of rejection—that is, unexplained fever or weight gain, lethargy, irritability, poor feeding, arrhythmia, gallop rhythm, or congestive failure—and confirmed by an appropriate response to treatment.

Intravenous methylprednisolone (10 mg/kg) for three days was given for rejection within the first six weeks. This was followed by oral prednisolone (1 mg/kg) which was generally tapered off over three to four weeks. Rejection occurring after the first six weeks was treated likewise with oral prednisolone unless it was severe, in which case steroids would be given intravenously. All our patients have responded to augmented steroids: we have not had to resort to antithymocyte globulin or OKT_3 or refractory rejection.

CORONARY ANGIOGRAPHY

Coronary angiography is performed electively at yearly intervals from the second year onwards.

STATISTICAL METHODS

Comparison of the ages of rejectors and non-rejectors was performed with the Mann–Whitney U test. Univariate analysis of rejection by age was with Fisher's exact test. Height SD score at transplant and one year after were compared using the Wilcoxon signed rank test. Statistical significance was taken at the 5% level. Actuarial survival was calculated according to the method of Kaplan and Meier.[6]

Results

After induction of immunosuppression, five patients did not receive any more steroids. All remaining children required pulses for rejection. Of these, two required a prolonged low dose prednisolone tail for continuing mild rejection: one is now off steroids and has remained free of rejection for six months, the other is currently still on prednisolone 0·1 mg/kg/day. Five patients did not tolerate azathioprine and are currently maintained on cyclosporin alone.

Table 2 illustrates early and late complications and survival data. Actuarial survival was 94% at one year. Thirteen episodes of rejection requiring treatment were diagnosed by echocardiography with or without endomyocardial biopsy (0·51

Table 2 Follow up data on paediatric cardiac transplant recipients

Case No	Ischaemic time (min)	Perioperative complications	Rejection episodes		Hypertension (late)	Renal function (ml/min/1·73 m²)	Survival
			<3 months	>3 months			
1	69	Staphylococcal septicaemia, gastroenteritis	—	—	No	148	3·8 years
2	89	—	1	—	No	54	3·4 years
3	210	CMV infection	—	—	No	57	3·1 years
4	206	—	1	—	No	86	2·1 years
5	168	—	1	—	Yes	71	1·9 years
6	220	Convulsions	—	—	No	83	1·7 years
7	170	Left hemiparesis	1	2	Yes	115	1·6 years
8	176	Donor failure	—	—	—	—	DOT
9	271	—	—	1	Yes	166	1·4 years
10	137	Hypertension	1	—	No	112	1·3 years
11	220	—	—	1	No	90	1·2 years
12	72	Hypertension, urinary tract infection	1	—	No	109	1·1 years
13	226	Bleeding (reoperated), fits (hypertensive encephalopathy)	1	1	Yes	91	12·5 months
14	184	Line sepsis, gastroenteritis	1	—	No	135	9·8 months
15	164	Hypertension, line sepsis	—	—	Yes	83	7·4 months
16	213	Hypertension	—	—	Yes	NA	79 days
17	173	PUO	—	NA	No	101·5	38 days

CMV=cytomegalovirus, DOT=died on table, NA=not applicable, PUO=pyrexia of unknown origin episodes/patient year); eight occurred within the first three months of OHT (0·17 episodes/patient month). Of 13 episodes of treated rejection, four were diagnosed on clinical and echocardiographic grounds alone. Endomyocardial biopsies were performed in the remaining nine episodes: moderate rejection according to the Billingham classification[7] was confirmed on four occasions, mild rejection on four, and minimal rejection on one occasion. Six patients (including three infants) never rejected. There was no significant difference between the mean age of the non-rejectors and that of the rejectors (4 *v* 5·5 years, p>0·05), nor was there any significant difference between the number of rejection episodes in the first month among the infants when compared with older children (p>0·05).

Paediatric OHT patients were admitted to hospital 3·54 times/patient year (fig 1). Most commonly, admissions were for the diagnosis of unexplained fever and the exclusion of rejection. The usual childhood infections were tolerated well, and did not appear to occur with undue frequency. Apart from a single episode of staphylococcal septicaemia in the perioperative period, life threatening infections have not been a problem.

By contrast, hypertension has been a significant early and late complication requiring treatment. Five children developed early postoperative hypertension, one complicated by hypertensive encephalopathy with convulsions. Not all of these children required long term antihypertensive treatment, however: two remained normotensive despite discontinuation of their treatment. The remaining three children, and three others who became hypertensive on follow up, required long term antihypertensive treatment.

Three children had impaired renal function as assessed by Barratt's formula, with an estimated GFR <80 ml/min/1·73 m^2 (table 2). All three children had normal preoperative renal function, although one child had documented reflux nephropathy.

Coronary angiography was performed on four children who have survived for two years or more. To date we have not detected any evidence of accelerated graft coronary disease.

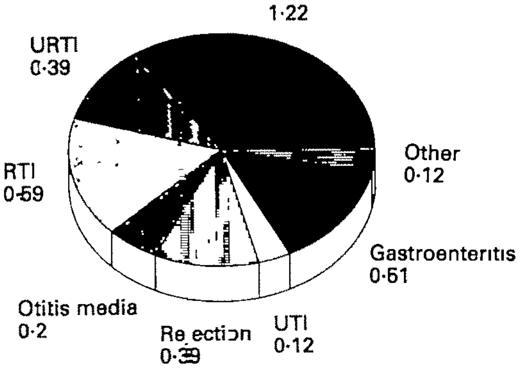

Figure 1 Hospital admissions for paediatric cardiac transplant recipients (linearised rate/patient year). PUO=pyrexia of unknown origin, RTI=respiratory tract (chest) infection, URTI=upper respiratory tract infection, UTI=urinary tract infection

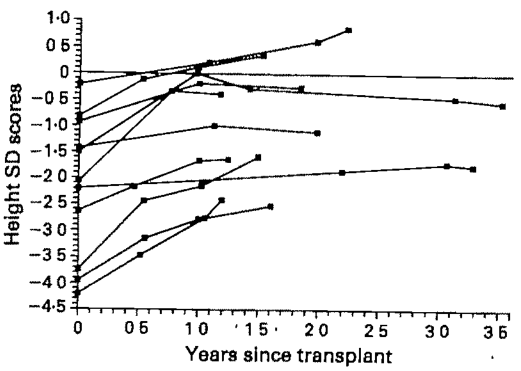

Figure 2 Growth after paediatric cardiac transplant.

Progressive changes in height SD score after OHT are shown in figure 2. All patients demonstrated an initial increase in height SD score, with the mean (SD) height SD score increasing significantly from −2·15 (1·35) to −1·15 (1·16) during the first year after transplantation (p<0·005). Mean (SD) height velocity during the first year was 10·3 (2·2) cm/year and height velocity SD score was 4·11 (2·03). Overall, patients with cardiomyopathy were taller before transplantation than patients with congenital heart disease (height SD score −1·48 (0·69) *v* −2·41 (1·48), and attained a smaller height velocity response during the first year after transplantation (height velocity 8·53 (2·56) *v* 10·99 (1·78) cm/year; height velocity SD score 3·32 (3·6) *v* 4·4 (1·34)). However, sample sizes are small and none of the differences achieved statistical significance. Likewise, a meaningful statement cannot be made regarding postoperative growth in patients who received pulsed steroids when compared with those who did not, as only one patient has been followed up for more than one year in the latter group. All patients currently enjoy a good quality of life, although one patient is showing significantly delayed psychomotor development.

Discussion

Yacoub *et al*, in 1985, reported initial results of steroid-sparing immunosuppression in 67 patients, with an actuarial survival rate of 82% at one year.[8] Subsequently, two prospective, randomised clinical trials have been performed in adults.[9 10] Both studies reported an increased incidence of rejection on a steroid-sparing regimen, with possible benefits in terms of a reduction in the incidence of hypertension, serious infections, and the development of diabetes. A recent survey of paediatric heart transplant practice in the USA showed that 74% of centres used steroid-based maintenance immunosuppression (cyclosporin, prednisolone, azathioprine), 17% used cyclosporin and prednisolone, and 26% used steroid-sparing regimens.[2] Since the inception of our paediatric cardiac transplant programme in 1987, we have adopted a steroid-sparing maintenance immunosuppression regimen, consequent upon our concern about the effects of steroids on growth and infection in this age group. We present in this report the medium term results of our regimen in 16 children who have survived orthotopic heart transplantation.

SURVIVAL

Of the 17 children, one died in the immediate postoperative period of primary donor organ failure. All other children in this series have survived OHT and are alive at current follow up. Actuarial survival at one year is 94%. The risk of paediatric OHT is documented to be higher than adult OHT: operative mortality is 24% in children ≤4 years and 16% in children 5–9 years.[1] Donor organ preservation failure, donor right heart failure associated with recipient pulmonary hypertension, difficulty in reconstructing complicated pulmonary artery anatomy, and haemorrhage are often responsible.[1 11] There seems to be general consensus that OHT is contraindicated if the pulmonary vascular resistance index (PVRI) is greater than 5–6 Wood units/m^2 despite pharmacological manipulation[12–14]; the risk becomes prohibitively high if this is associated with preoperative inotrope dependency.[12] The majority of our patients with congenital heart disease had a 'protected' pulmonary circulation by virtue of their pulmonary artery banding or pulmonary stenosis, and only one of our patients with cardiomyopathy had a PVRI of >6. These factors may explain at least in part our excellent operative mortality. On the other hand, we have not had any technical deaths attributable to previous pulmonary artery banding (four children) or systemic-pulmonary shunting (three children).

REJECTION

Table 3 compares the linearised incidence of rejection in our patients with those figures published by other centres. The different series are not directly comparable, as the age composition of the patient groups is different and the method of rejection surveillance dissimilar. Nevertheless the various incidences are within the same order of magnitude, regardless of whether steroid-sparing or steroid-based maintenance immunosuppression was employed. The real question is whether the tendency to reject is the same in infancy, childhood, and adolescence. Animal experiments suggest that the host immune response is less aggressive and more easily controlled shortly after birth, and clinical observations have confirmed that the newborn infant (0–30 days) may be immunologically the best possible recipient of a cardiac allograft.[16] Other workers have reported that rejection occurred more commonly in adolescents than in children and infants,[17] although we have not found a significant difference in the frequency of rejection between infants and older children. We have, however, experienced difficulty in weaning two of our older children from steroids after augmented immunosuppression for rejection, and other workers have had similar experiences.[11 18] Significantly, late deaths from rejection have been reported in most published series involving older children[11 17 19] but not infants.[15 20 21] These observations support the concept of a 'window of opportunity' in neonatal,[22] and perhaps early childhood transplantation, which may be reflected by the satisfactory control of rejection with a less aggressive immunosuppressive regimen.

Table 3 Linearised rejection incidences in published series

Series	*Mean age*	*Episodes/patient month*		*Immunosuppression regimen*	*Rejection surveillance*
		1st month	*1st 3 months*		
Current	3·8 years	0·38	0·17	CA	Non-invasive
Loma Linda[15]	1·8 months	0·82	0·71	CA/C	Non-invasive[*]
Pittsburgh[11]	9 years	0·7	—	CPA	?
Stanford[14]	7·4 years	0·67	(0·34)†	CPA	Biopsy

C=cyclosporin; A=azathioprine, P=prednisolone.
[*]First year of life only, biopsy thereafter, †third month

LATE COMPLICATIONS

The most frequent late complications in paediatric OHT are infection, hypertension, renal impairment, and growth retardation.[19] Of greater concern, although occurring less frequently, are malignancies and coronary artery disease.

In common with some other published series[17 19 20] there were no late deaths due to infection in our patients. However, this cannot be attributed to our steroid-sparing maintenance regimen as similar results have been reported with steroid-based maintenance immunosuppression.[17 19] Minor infections and undiagnosed fever were common reasons for hospital admissions among our patients. These admissions were more precipitated by the spectre of rejection and overwhelming infection than the severity of the illness, and it is pertinent to note that neither has been a problem beyond the first year. Nevertheless, two children have had troublesome and persistent chest infections requiring recurrent admissions and prolonged courses of antibiotics. Like others, we have not noted a greater frequency of minor ailments in our patients over that of children in the general population.[23]

Hypertension is a common adverse effect of cyclosporin treatment,[3] which may be potentiated by steroids.[24] It has been reported to occur in 40–96% of children undergoing OHT.[18 19] Our experience is in accord with the former figure. Nephrotoxicity is another common adverse effect of cyclosporin,[25] although long term renal impairment may not be as great a problem as feared.[16 18 26] Indeed, a recent report suggests that renal function can be preserved in paediatric patients if the whole blood trough concentration was maintained between 100 and 200 ng/ml.[27] However, all three children with estimated GFR <80 ml/min/1·73 m^2 in our series had normal preoperative renal function, although one had documented reflux nephropathy.

At the time of OHT, our patients were substantially shorter than normal. This may be due to the multifactorial, though well recognised, adverse effect of cardiac failure on growth.[28] In all our patients in whom adequate growth data is available, catch-up growth is observed during the first year after transplantation. While surgical correction of congenital heart disease frequently improves growth[29] there is limited and conflicting data on the effects of OHT. With steroid-based maintenance immunosuppression, some groups have reported growth retardation in up to 75% of children younger than 14 years,[26] while others have demonstrated normal growth after transplantation.[11 19] The use of steroids for cumulative periods of more than one month, at two or more times the physiological replacement dose, has been implicated in those children with unsatisfactory growth after transplantation.[30] Therefore, the use of a steroid-sparing maintenance immunosuppression regimen may in part explain the excellent initial growth response observed in our patients after OHT. Nevertheless, after the first year, our patients as a group remain shorter than normal, and the catch-up effect appears to wane. Further analysis of the data is limited by the lack of bone age measurements: it remains to be seen with prolonged follow up whether these children have a normal growth potential, but with some constitutional delay.

Finally, the occurrence of accelerated arteriosclerosis and lymphoproliferative diseases in paediatric OHT patients is well established,[11 19 31] although we have not, as yet, noted either in our patients. The use of steroids may theoretically contribute to the former,[3] while the use of cyclosporin and azathioprine is known to be associated with the latter. It remains to be seen whether a steroid-sparing maintenance immunosuppression regimen will result in reduced graft coronary artery disease in this age group, although there is evidence in adults that this may be so.[32]

CONCLUSION

These results confirm that a steroid-sparing maintenance immunosuppression regimen consisting of cyclosporin and azathioprine can be successfully used in paediatric OHT, with acceptable early and late morbidity. Potential benefits include improved growth. Further follow up is required to determine if this regimen results in a reduced incidence of accelerated graft coronary artery disease.

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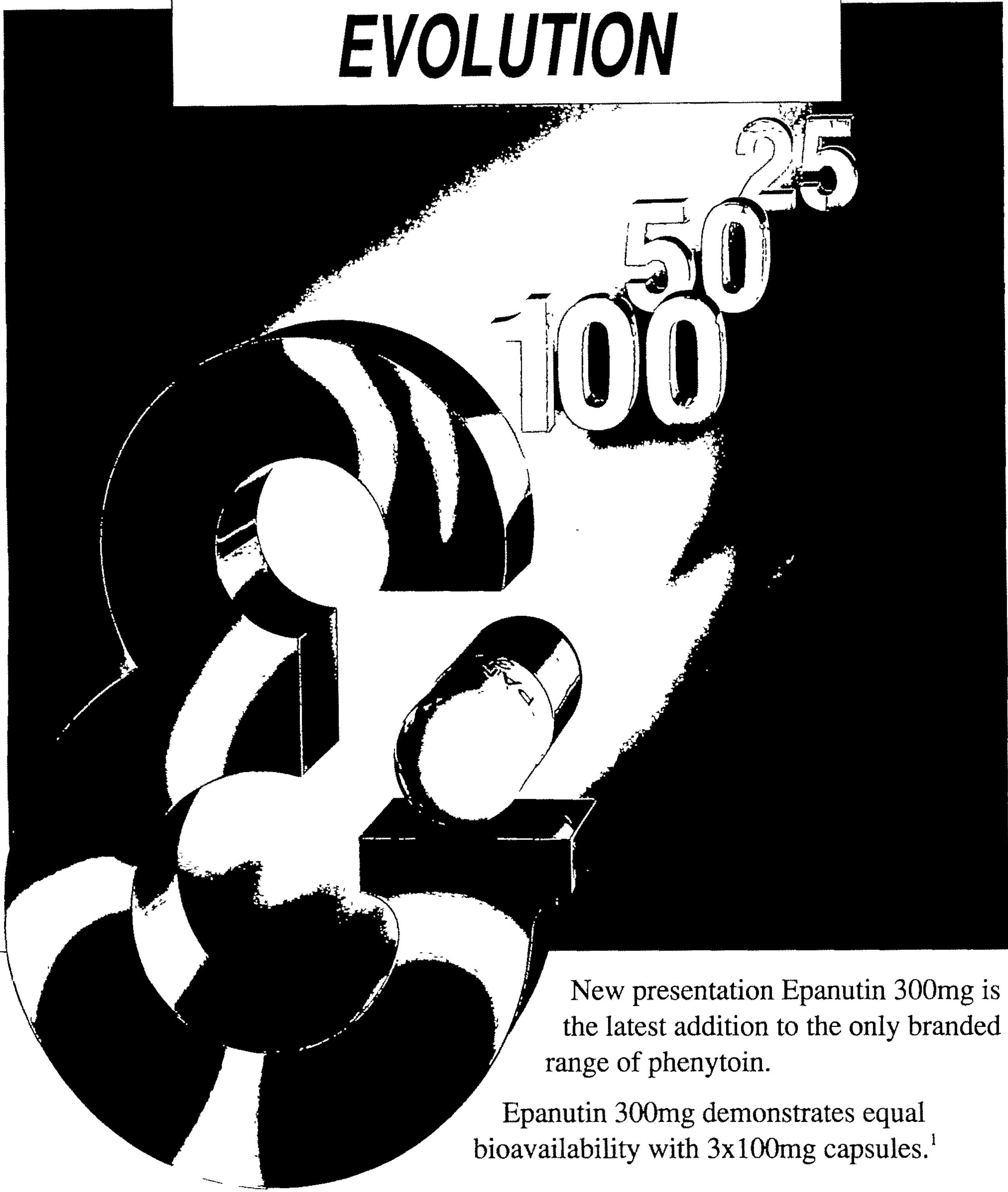
EVOLUTION



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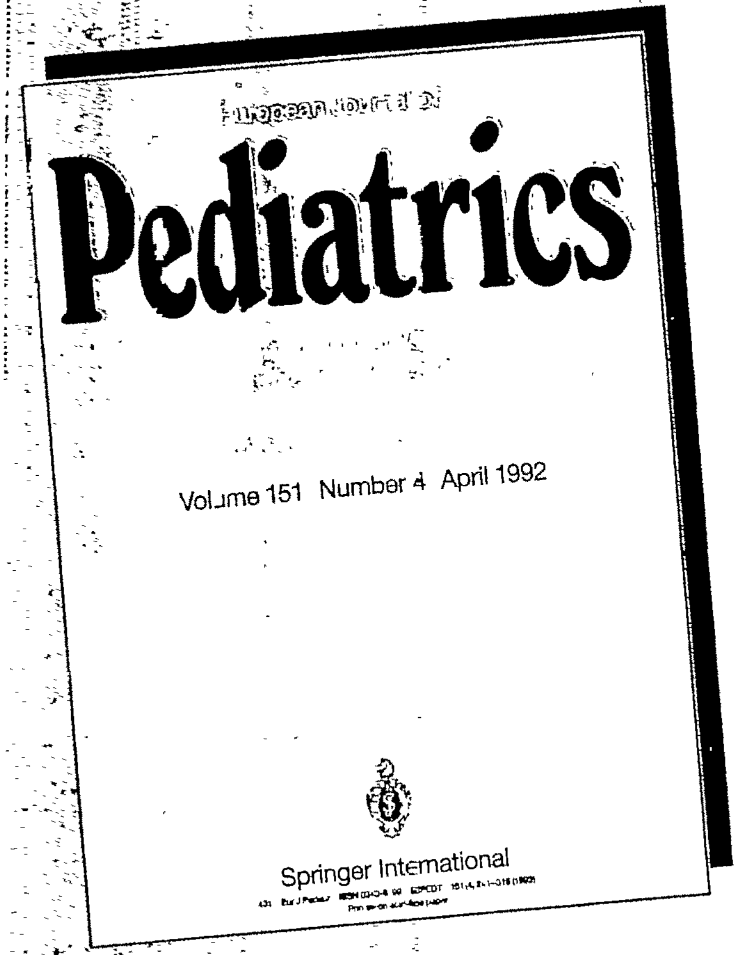

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Intravenous immunoglobulin in HIV-I infected haemophilic patients

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Abstract

In order to evaluate the efficacy of intravenous immunoglobulin (IVIG) in the early stages of HIV infection (patients without AIDS or AIDS related complex) a prospective controlled open trial was conducted in 36 patients (age 6–19 years) with haemophilia. Eighteen patients received 0·3 g/kg IVIG at two week intervals; 18 patients served as controls. Major criteria for the evaluation were progression of HIV disease assessed by the modified Brodt/Helm classification, number of infectious events and HIV associated thrombocytopenia, and the CD4+ T cell count. After 24 months of evaluation seven patients in the IVIG group and five patients in the control group deteriorated according to their staging, with one patient in each group developing AIDS. Thrombocytopenia and infectious events, but no severe bacterial infections, occurred in both groups in similar numbers. The absolute CD4+ T cell count decreased by 284/μl in the IVIG group and by 143/μl in the control group respectively (mean values). The statistical analysis of these criteria did not reveal any significant difference.

In conclusion, IVIG was not effective in the early stages of HIV infection in patients with haemophilia. IVIG did not slow down the progression of HIV disease and did not prevent the development of an immunodeficiency as assessed by the CD4+ T cell count.

(*Arch Dis Child* 1992;67:1267–71)

A large proportion of patients with haemophilia acquired HIV-I infection because of the use of commercial clotting factor concentrates that had not been virus inactivated.[1] As in other risk groups, HIV infection in patients with haemophilia often leads to deterioration of the immune system and results in AIDS with opportunistic infections.[2 3] The progression of HIV infection in paediatric patients with haemophilia is evident but runs a slower course when compared with the progression in adult HIV infected patients with haemophilia.[4 5] Paediatric AIDS is more often associated with bacterial infections than it is in AIDS in adults.[6]

The efficacy of intravenous immunoglobulin (IVIG) in primary immunodeficiencies like agammaglobulinaemia and common variable immunodeficiency is well established.[7] The application of IVIG is largely safe with regard to the frequency of anaphylactic and non-anaphylactic reactions, as well as regarding the transmission of infectious agents.[8] During recent years, the use of IVIG has been extended to diseases in which a possible immunomodulatory effect of IVIG could be of advantage. Examples of this application of IVIG include the management of idiopathic thrombocytopenic purpura, Kawasaki syndrome, and certain forms of rheumatic disorders.[9]

The use of IVIG in paediatric AIDS was first shown to be effective in 1986, resulting in a decreased number of bacterial infections and in an increase of CD4+ T cells.[10] A more recent multicentre trial studying IVIG application in symptomatic HIV disease in children showed a significantly increased time free of severe bacterial infections in the treatment arm, but no effect on mortality was observed.[11] In the latter study patients with haemophilia were not included.

Therapeutic approaches to HIV infection have changed from treating the clinical manifestations of AIDS only to the development of prophylactic regimens with early use of antiretroviral, antibiotic, and antifungal drugs in an attempt to delay the immunological deterioration and to prevent episodes of opportunistic infections. In this controlled prospective open trial, we studied the effects of IVIG in early stages of HIV infection (patients without AIDS or AIDS related complex) in haemophilic children and adolescents during a 24 month period.

Patients and methods

INCLUSION CRITERIA

Confirmed diagnosis of HIV infection in patients with haemophilia A or B, persistent generalised lymphadenopathy (according to the definition of the Centers for Disease Control, CDC, Atlanta), or a CD4+ T cell count of <35% of lymphocytes were the criteria used for inclusion in the study. No patients already suffering from AIDS or AIDS related complex (CDC criteria) were included.

Thirty six male patients aged 6 to 19 years (mean age 14·8 years) fulfilled these criteria and were enrolled in the study. The patients or their parents gave their informed consent. For the evaluation matched controlled pairs of patients were formed. All pairs were matched by age and stage of HIV infection. One patient from each pair received IVIG and the other patient received observation only. Eleven pairs (22 patients) were randomly assigned to the treatment or the control group; in seven pairs (14 patients) the patients were assigned to one of the arms according to the patient's or his parents request to receive IVIG or to belong to the control group. At the time of entry no patient had previously been treated with IVIG or antiretroviral drugs.

IVIG APPLICATION

Patients on the treatment arm were given 0·4 g/kg IVIG (Venimmun, Behringwerke AG) on four consecutive days followed by 0·3 g/kg IVIG at 14 day intervals. On average, the IVIG infusions lasted a mean (SD) of 2·9 (0·6) hours. The study was designed for an evaluation period of 24 months. According to the guidelines of the Bundesministerium fuer Frauen, Familie, Jugend und Gesundheit, of the Federal Republic of Germany, adverse effects were directly reported to the study centre and evaluated for the necessity of terminating the IVIG application.

EVALUATION CRITERIA FOR THE EFFICACY OF IVIG

The major criteria for studying the effects of IVIG were the progression of disease stage according to the Brodt/Helm classification,[12] the incidence of infectious events and HIV associated thrombocytopenia (defined as a platelet count $<100\times10^9$/l), and the CD4+ T cell count. In addition to the opportunistic infections fulfilling the AIDS case definition of the CDC, the following were also included as infectious events: fever of unknown origin for more than one week, recurrent diarrhoea of more than three stools per day for more than one week, herpes zoster, oral candidiasis, pneumonia, bronchitis, sinusitis, and otitis media. The Brodt/Helm classification was used because it does not take account of the patient's age. This is in contrast to the CDC classification system, which would have divided our study group into two different classifications (that is patients above and below 13 years of age) and thus would have complicated the comparison between the study arms. As shown in table 1, the Brodt/Helm classification was modified for this study by using the ratio of CD4+ T cells to lymphocytes (this is *not* the ratio of CD4+ T cells to CD8+ T cells), which has been shown to be a reliable prognostic indicator of immunological deterioration in HIV infection.[5 13] During the study physical and laboratory examinations of the patients were performed at the entry and at three month intervals thereafter.

LABORATORY TESTS

The following laboratory tests were performed at three month intervals: red cell count, white cell count, measurement of the erythrocyte sedimentation rate (in mm in the first hour), liver function tests including alanine aminotransferase and glutamyltransferase by conventional commercial tests (Boehringer), and IgG, IgA, and IgM by nephelometry. Peripheral lymphocyte subpopulations were assessed by flow cytometry using commercial monoclonal antibody reagents (obtained from Ortho Diagnostics or Becton Dickinson). In case of illness additional diagnostic work-up was performed as clinically indicated: chest radiography, ultrasonography of the abdomen, electroencephalography, microbiological studies and cultures of blood, spinal fluid, throat swabs, stool, and urine.

Table I Modified Brodt/Helm classification of HIV infection

Stage	*Definition*
1a	Healthy seronegative subject at risk of HIV infection
1b	Healthy seropositive subject, no immunodeficiency
2a	Seropositive patient with lymphadenopathy syndrome or CD4+ T cells <25% (of lymphocytes)
2b	Seropositive patient with severe immunodeficiency and a CD4+ T cell count of <350/µl or <20% (of lymphocytes)
3	AIDS (CDC definition)

STATISTICS

The structural similarity of the IVIG group and the control group was verified for the age of the patients and the CD4+ T cell count at entry by Student's *t* test and for the initial staging according to the Brodt/Helm classification by Bowker test.[14] The above listed main criteria to investigate the efficacy of IVIG were considered by the Wilcoxon-Mann-Whitney test and Bowker test. After six and 12 months, interim analyses were performed with increasing significance levels.[15] Herein the significance levels were 0·5% for the first interim analysis after six months, 1·4% for the second interim analysis after 12 months, and 4·5% for the analysis at the end of the study.

ETHICS

This study was performed according to the permission of the ethics committee of the medical faculty at the University of Bonn.

Results

IVIG APPLICATION AND ADVERSE EFFECTS

The evaluation period was a mean (SD) of 24·0 (2·3) months in the IVIG group and 24·4 (1·7) months in the control group. In five patients one to two infusions were missed during the course of the study. In total, 1018 IVIG infusions were given. In 35 of these 1018 infusions adverse effects were reported. These consisted of headache, nausea, vomiting, fever, and urticaria. No anaphylactic reaction occurred. With the exception of one patient, who was treated with antihistamines and corticosteroids for a non-anaphylactic reaction, no therapeutic interventions were necessary. In four cases the single infusion was stopped due to the adverse reaction. There was no case in which the necessity to discontinue the study was found.

Two patients in the IVIG group and three patients in the control group were begun on zidovudine due to an immunological deterioration during the study period. Four of these five patients also received inhaled pentamidine as primary or secondary prophylaxis of *Pneumocystis carinii* pneumonia.

PROGRESSION OF HIV DISEASE

One 13 year old patient in the IVIG group developed AIDS (*P carinii* pneumonia) after 12 months of the study and died of cardiac failure after 22 months. A 6 year old patient in the control group also developed AIDS (wasting syndrome) and died one month after completion of the study.

According to the modified Brodt/Helm classification (table 1) one patient in the IVIG group improved, 10 patients did not change their staging, and seven patients showed a progression of their disease during the 24 months evaluation period. In the control group two patients improved, 11 patients remained stable, and five patients deteriorated. There was no statistically significant difference detected between the two groups (Bowker test, p>0·05). Table 2 summarises these data.

Table 2 Progression in staging in the IVIG group versus the control group assessed by the modified Brodt/Helm classification of HIV infection

Staging at entry and after 24 months	*IVIG group (n=18)*	*Control group (n=18)*
2b to 2a	1	2
2a to 2a	7	7
2b to 2b	3	4
2a to 2b	6	4
2b to 3	1	1

Table 3 Infectious events in the IVIG group versus the control group during 24 months evaluation period

Infectious events	*IVIG group (n=18)*	*Control group (n=18)*
Otitis media	6	10
Bronchitis, acute	5	4
Infectious diarrhoea	4	1
Oral candidiasis	1	3
Herpes zoster	1	2
Sinusitis	2	1
Pneumonia	1	1
P carinii pneumonia	1	0
Fever of unknown origin	1	0

INFECTIOUS EVENTS AND HIV ASSOCIATED THROMBOCYTOPENIA

As outlined in table 3, most infectious events that occurred were of minor severity with the exception of the one case of *P carinii* pneumonia. In both groups, 22 infectious events were counted. At least one episode of HIV associated thrombocytopenia developed in five patients in the IVIG group and in three patients in the control group. One patient in the IVIG group and two control patients remained thrombocytopenic during the study; the IVIG treated patient experienced recurrent petechiae and epistaxis despite treatment with zidovudine as well. Overall there was no significant difference in the occurrence of infectious events and thrombocytopenia between the two groups (Wilcoxon-Mann-Whitney test, p>0·05).

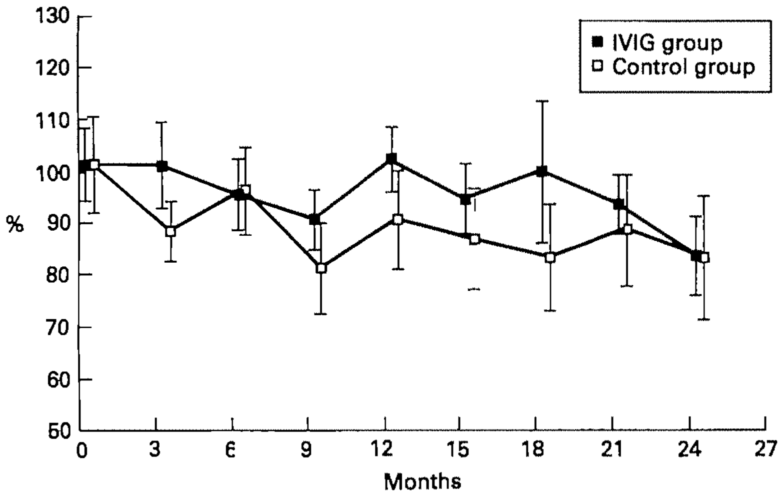

Figure 1 Changes in the ratio of CD4+ T cells to lymphocytes during 24 months represented as mean (SE) percentage of the initial values.

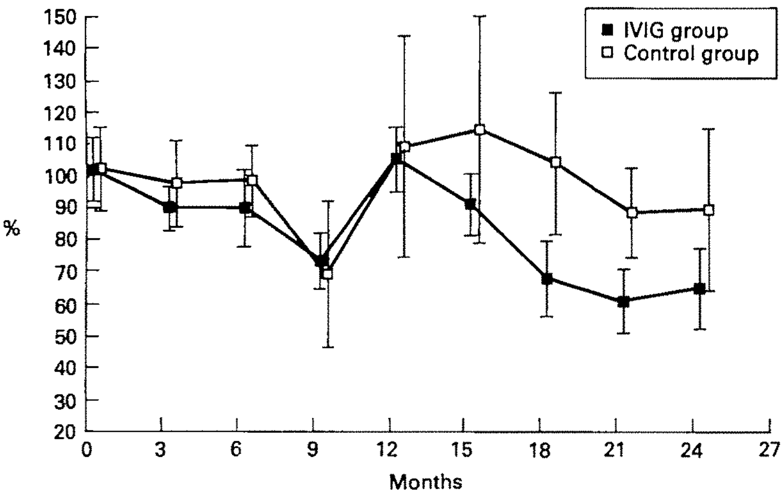

Figure 2 Changes in the absolute CD4+ T cell counts during 24 months represented as mean (SE) percentage of the initial values.

CD4+ T CELL COUNT

The absolute count of the CD4+ T cells was a mean (SE) of 663 (67)/μl for the IVIG group at the beginning of the study; the corresponding ratio of CD4+ T cells to lymphocytes was 0·241 (0·017). After 24 months these parameters declined to a mean (SE) of 379 (56)/μl and to 0·212 (0·018) respectively. Thus the absolute CD4+ T cell count decreased by a mean (SE) of 284 (67)/μl and the ratio of CD4+ T cells to lymphocytes decreased by 0·029 (0·013). In the control group the absolute CD4+ T cell count was a mean (SE) of 730 (98)/μl initially and declined to 586 (76)/μl after 24 months; this represents an average decrease of 144 (99)/μl. The ratio of CD4+ T cells to lymphocytes decreased by a mean (SE) of 0·038 (0·019) from 0·246 (0·023) initially to 0·208 (0·023) at the last examination. The difference between the mean changes in the two groups was a mean (SE) of 140 (119)/μl referring to the absolute CD4+ T cell count and was 0·009 (0·023) referring to the ratio of CD4+ T cells to lymphocytes. In figs 1 and 2 the data of the CD4+ T cell counts (ratio and absolute count) are represented as percentages of the initial values.

The statistical comparison (Wilcoxon-Mann-Whitney test) did not result in a significant difference for either the absolute CD4+ T cell count (p=0·275) or for the ratio of CD4+ T cells to lymphocytes (p=0·799).

IgG

In the IVIG group mean (SE) IgG concentrations in sera were 23·14 (1·65) g/l at the beginning and 23·16 (2·09) g/l after 24 months respectively. IgG concentration in sera of the control group were 22·16 (2·84) g/l at the entry and 21·38 (2·26) g/l at the last examination.

Discussion

To our knowledge this is the first prospective controlled study dealing with the efficacy of IVIG application in the early stages of HIV infection in haemophilic patients. The adverse reactions reported here that accompanied the administration of IVIG were of non-anaphylactic character, and did not lead to discontinuance of the study in any patient. Usually these side effects could be avoided by slowing down the infusion rate. These adverse reactions have been previously well described elsewhere.[6 17] This study was performed in haemophilic patients classified as having early stages of HIV infection. Patients already suffering from AIDS or AIDS related complex were excluded from the study in order to detect specifically whether there is a measurable therapeutic benefit with early use of this interventional regimen. As shown in table 2 there was a considerable progression of HIV disease in both groups during the 24 months. In the IVIG group seven of 18 patients (38%) worsened according to the Brodt/Helm classification compared with five of 18 patients (28%) in the control group. In each group one patient developed AIDS. The patient in the IVIG group died during the study, the patient in the control group died four weeks after completion of the study. In conclusion, any benefit of the IVIG treatment in delaying disease progression as assessed by the staging of the patients was not detectable. At the beginning of the study no patient received antiretroviral drugs or antibiotics. Due to immunological deterioration, and the in between established efficacy of zidovudine as an antiretroviral agent and of pentamidine for prophylaxis against *P carinii* pneumonia, these regimens were initiated in five patients. As these patients were rather equally distributed between the two groups, this should not lead to a major bias. We can not rule out, however, that the institution of these drugs outweighs a potential benefit of IVIG.

To date, there has been no published study dealing with IVIG application in HIV infection in haemophiliacs. Therefore the results must be compared with studies of IVIG treatment in other risk groups. The National Institutes of Health multicentre trial in children with vertically transmitted symptomatic HIV infection did not result in a lower mortality in the IVIG group.[11] Other reports, however, showed appreciable improvement of neurological symptoms such as psychomotor development and other clinical symptoms, such as lymphoid interstitial hyperplasia not directly related to bacterial infections; unfortunately, these studies lacked a control group.[18 19]

Bacterial infections are a major cause of illness in paediatric AIDS or AIDS related complex.[6 20 21] In this study only mild infections occurred in both groups during the 24 months, with the exception of the one case of *P carinii* pneumonia. This may be due to the onset of the study in early stages of HIV infection. In addition, most haemophilic patients in this study were infected with HIV after their first years of life, compared with the prenatal or perinatal infection in vertical transmission of HIV. For this reason the patients in this study may be even more representative of the adult type of HIV infection, where the virus encounters an already developed immune system. It is possible that an evaluation period beyond 24 months could eventually lead to the observation of a benefit of IVIG treatment. However, any potential benefit must be balanced against the inconvenience and the time involved in the administration of the drug.[22] The National Institutes of Health study clearly demonstrates the efficacy of IVIG in the reduction of bacterial infections and number of hospitalisations in prenatally or perinatally HIV infected children. But this effect was limited to the patients with more than 200 CD4+ T cells/μl, whereas in the patients already presenting with a CD4+ T cell count below 200/μl at entry this benefit was not evident.[11] In addition, another study conducted earlier but lacking a control group also reported a reduction in the number of infectious episodes.[23]

The number of CD4+ T cells represents an important prognostic indicator[5 13] and therefore is a useful laboratory tool to identify the immunodeficiency developing in HIV infection. In this study the absolute CD4+ T cell count and the ratio of CD4+ T cells to lymphocytes were assessed at three month intervals. Both parameters declined in the two groups as shown in figs 1 and 2. In addition both parameters showed a high standard error. This may be a reflection of our relatively small sample size. No statistically significant difference was detectable, so IVIG did not lead to a delay in the development of immunodeficiency when assessed by the CD4+ T cell count. In another study the number of patients whose CD4+ T cell count improved during IVIG treatment was reported to be significantly higher than in the control group, but no details are available regarding the comparibility of the study groups and regarding the method of patient assignment to any of the study groups.[10] The end points of the National Institutes of Health study did not include the CD4+ T cell count.[11]

This prospective, controlled study was conducted in order to evaluate the efficacy of IVIG in early stages of HIV infection in haemophilic patients. In conclusion, after 24 months no significant effect was detected in comparison with the control group as assessed by (1) the progression of HIV disease defined by the modified Brodt/Helm classification, (2) the number of infectious events and occurrence of HIV associated thrombocytopenia, and (3) the CD4+ T cell count. Whether there is a benefit of IVIG after manifestation of AIDS in haemophilic patients cannot be concluded from these data and needs further evaluation.

This study was in part presented on the Seventh International Conference on AIDS, Florence, 1991.

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Gastrointestinal complications of gastrocystoplasty

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Abstract

The cases are reported of five children with chronic renal failure who underwent gastrocystoplasty for a variety of urological disorders. Gastrocystoplasty comprises the transplantation of a vascularised segment of stomach to the bladder to form an augmented neobladder. The patients had gastrointestinal complications after the operation, including considerable weight loss in all five patients, accompanied by marked failure to thrive in four of the five patients, and food aversion, feeding intolerance, dumping syndrome, delayed gastric emptying, and oesophagitis in two patients. Three of the five patients developed severe abdominal pain and haemorrhagic cystitis secondary to gastric acid secretion in the neobladder from the transplanted gastric pedicle. Nutritional and pharmacological interventions were used to manage the gastrointestinal problems. Explanations are offered for the pathophysiology of the observed complications of gastrocystoplasty. It is believed that the use of this procedure in infants and children, particularly those with chronic renal failure and uraemia, warrants caution until successful long term follow up and experience with this procedure have been reported.

(*Arch Dis Child* 1992;67:1272–6)

Gastrocystoplasty is a technique that uses a vascularised segment of the stomach to replace or augment the urinary bladder. The more common use of ileal, caecal, jejunal, and colonic segments for this purpose has been well described.[1 2] Two major series have been reported for the use of gastrocystoplasty in children.[3 4] Bladder augmentation is most often used after cystectomy in adults who have tuberculosis of the bladder or bladder carcinoma,[1] and in children who have urodynamic dysfunction (such as neurogenic bladder or bladder outlet obstruction).[1 5–7] The most common urodynamic disorder in children that requires bladder augmentation is a trabeculated, low compliance bladder, which often occurs in boys with posterior urethral valves and chronic vesicoureteral reflex.[8]

Owing to the potential metabolic disturbances[9] and nutritional consequences of using bowel segments,[10] the use of stomach segments for bladder augmentation has been suggested. Although this technique has been studied in two types of animal model,[11] the complications of this operation in children and adults have not been described. This paper describes the gastrointestinal complications after gastrocystoplasty in five children and addresses the management of these patients.

Case reports

Gastrocystoplasty, as a form of bladder augmentation and an alternative to more conventional bladder augmentation techniques, was performed on five children with different urological dysfunctions at The Hospital for Sick Children, Toronto, Ontario, from 1987 to 1991. This operation comprised 5% of the total of 90 bladder augmentations performed at our institution during this period. These five children (three boys, two girls) ranged in age from 20 to 84 months. All five children had chronic renal impairment, and two were receiving haemodialysis at the time of the operation. The patients reported no underlying gastrointestinal or nutritional symptoms before gastrocystoplasty. All five patients had failure to thrive four to six months after gastrocystoplasty.

PATIENT 1

A 10 month old girl with urogenital sinus anomaly, cloacal extrophy, dysplastic kidneys, and a small bladder, which led to her initial bladder augmentation, a gastrocystoplasty, subsequently developed intermittent acidosis and alkalosis, and continued to have a low compliance, low volume bladder necessitating a second bladder augmentation, this time an ileocystoplasty. Nissen fundoplication was also performed during the ileocystoplasty because she developed refractory gastro-oesophageal reflux after gastrocystoplasty. Four months after the operation she developed cyclic vomiting, dumping syndrome, and food aversion. Investigations included an upper gastrointestinal series, a technetium-99 gastric emptying scan, a feeding study with fluoroscopy, preprandial and postprandial blood glucose monitoring, and upper endoscopy with biopsy sampling. Table 1 lists the findings and therapeutic interventions.[12] After treatment, her dumping syndrome and food aversion resolved, and the patient showed appropriate weight gain.

PATIENT 2

A 54 month old boy with a small non-compliant bladder, who was receiving haemodialysis for renal failure secondary to posterior urethral valves, became anephric at gastrocystoplasty. After the operation he had severe abdominal pain, dysuria, haematuria, and hyperchloraemic

Table 1 Renal function, weight before and after surgery, and findings and treatment after gastrocystoplasty

Data	*Patient 1*	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*
Glomerular filtration rate (ml/min/1·73 m^2)*	35	<10 (prenephrectomy)	<10	17	45
Weight (kg) before/after† surgery	7 9/7·4	12·6/11 6	18·0/17·0	15 5/14·7	17·8/16·0
Findings	Rapid gastric emptying, postprandial hyper/hypoglycaemia, endoscopy showed short straight stomach and antrum absent, normal biopsy samples	Haemorrhagic cystitis acidic intrabladder pH	Normal to rapid gastric emptying, small stomach, narrow deformed antrum, mild gastritis, severe oesophagitis	Haemorrhagic cystitis, acidic intrabladder pH	Haemorrhagic cystitis, acidic urine pH
Treatment	Small frequent feedings by mouth, addition of cornstarch and medium chain triglyceride oil, continuous nasogastric overnight feeds, daytime nasogastric bolus feeds	Bladder irrigation with bicarbonate, ranitidine, omeprazole	Short term total parenteral nutrition, cisapride and ranitidine	Bladder irrigation with bicarbonate, ranitidine	Omeprazole

*Approximate glomerular filtration rate calculated with the Schwartz method; values given are for before the gastrocystoplasty (reference normal value at this institution >100 ml/min/1·73 m^2).[13]

†Four to six months after gastrocystoplasty.

alkalosis. Investigations included cystoscopy, and intragastric and intrabladder pH measurements. His suprapubic pain was consistently associated with a bladder pH of less than 2, and the resolution of symptoms was associated with an increase in bladder pH (table 2). He initially received ranitidine and intrabladder bicarbonate irrigation, but the pH decreased two hours after bicarbonate irrigation and his symptoms resumed (tables 1 and 2). Sucralfate bladder irrigation was not successful because of intrabladder concretions. Treatment with omeprazole gave a resolution of symptoms, maintenance of normal intrabladder pH, and an increase in intragastric pH (table 2), with an increase of gastrin in serum samples to 3105 ng/l (reference range 0–75 ng/l). He has gained weight appropriately, but has required maintenance treatment with omeprazole for symptomatic relief despite renal transplantation and a glomerular filtration rate of 74 ml/min/1·73 m^2.

PATIENT 3

A 62 month old boy with a small non-compliant bladder, who was receiving haemodialysis for renal failure secondary to posterior urethral valves, underwent an unsuccessful gastrocystoplasty and subsequent ileocystoplasty. He subsequently developed food aversion, nausea, vomiting, and early satiety, in addition to hypoalbuminaemia (albumin concentration 24 g/l) without significant proteinuria. Investigations included upper gastrointestinal series and upper endoscopy with biopsy sampling (table 1). The patient gained weight adequately after therapeutic intervention and had no additional gastrointestinal disorders at follow up.

PATIENT 4

Four months after gastrocystoplasty for a neurogenic bladder this 80 month old boy with Vater association developed abdominal pain and haematuria. Investigations included cystoscopy and intrabladder pH measurements (tables 1 and 2). This patient did not receive omeprazole as he found his symptoms tolerable with ranitidine and intrabladder bicarbonate irrigation (table 2). Six months after treatment had begun it was discontinued without recurrence of symptoms.

PATIENT 5

A 40 month old girl with urogenital sinus anomaly, high cloacal anomaly, anomalous ureteric implantation, small kidneys, and a small bladder, underwent gastrocystoplasty during genitourinary tract reconstruction. Three months after her gastrocystoplasty, she developed severe lower abdominal pain and bladder spasm, with symptoms intensifying 30 minutes to one hour postprandially. Neither cystoplasty nor other investigations were performed. Omeprazole (10 mg/day) successfully resolved her symptoms; her urine pH three days after treatment with omeprazole was 4·2. A pH

Table 2 Intrabladder and intragastric pH before and after treatment

pH	*Patient 2 (anuric)*	*Patient 4*
Intrabladder pH* before treatment	0·5–2·0 with GI and GU symptoms‡	1 0–1·5 with GI and GU symptoms‡
Intrabladder pH one hour after bladder irrigation with bicarbonate	5·5–8·0 without symptoms	6·0–7 5 without symptoms
Intrabladder pH two hours after bladder irrigation with bicarbonate	1·5–2·0 with GI and GU symptoms	2 5–3·0 with minimal symptoms
Intrabladder pH after treatment with omeprazole	5 0–7·0 without symptoms	Not applicable
Intragastric pH† after treatment with omeprazole	4 5–6·0	Not applicable

*Intrabladder pH obtained by catheterisation.

†Intragastric pH obtained by nasogastric tube

‡GI=gastrointestinal; GU=genitourinary

value for urine free of omeprazole has not been obtained. She is still being treated with omeprazole for symptomatic relief after two unsuccessful attempts to discontinue the drug.

Discussion

Although bladder augumentation with part of the gastrointestinal tract was described nearly 100 years ago,[1] descriptions of the sequelae of this procedure, particularly gastrointestinal tract complications, have been difficult to find. Furthermore, bladder augmentation effects on nutritional status have only recently been reported showing no long term changes in vitamin B-12, carotene, and albumin concentrations.[10] Metabolic complications after enterocystoplasty, such as chronic acidosis and rickets, have been described in children,[14] and hyperchloraemic metabolic acidosis and diminished acid challenge capacity have been described in children and animal models of bladder augmentation.[5, 11]

Using a canine bladder augmentation model, Piser *et al* showed a net reabsorption of chloride, ammonia, phosphate, and sodium in animals who underwent colocystoplasty compared with those who underwent gastrocystoplasty.[11] Guan *et al*, using Long-Evans rat species, studied the short and long term effects of ileal, colonic, and gastric segment cystoplasties.[15] They found that all voiding parameters, renal function, and biochemical profiles remained normal; levels of mucus production in the neobladder were higher in patients with gastrocystoplasty and colocystoplasty than in those with ileocystoplasty; and uroepithelialisation of the graft occurred, with native transitional epithelium extending over the junctional margin of the graft and covering the enteropatch mucosa as seen at necropsy.

The effect of chronic renal failure on bladder augmentation with stomach rather than sigmoid colon segments has been reviewed in the canine study by Kennedy *et al*.[16] Their results indicate that gastrocystoplasty is a superior technique for the treatment of the azotaemic canine. These animals tolerated significantly greater acid loading and did not have the hyperchloraemic acidosis and weight loss of the other animals who underwent enterocystoplasty.

Reports of bladder augmentation in children, including gastrocystoplasty, have not addressed the gastrointestinal complications that seem physiologically inherent in this procedure. Adams *et al*, in the largest series to date, described 10 patients undergoing gastrocystoplasty who had no sequelae or complications.[17] Follow up however, occurred only at one and three months, less than the average follow up interval (five months) for our series, at which time complications became apparent and clinically significant. In addition, Adams *et al* did not measure glomerular filtration rate, a more accurate indicator of renal function, making less clear the degree of renal compromise existing in their patients before and after gastrocystoplasty.[17]

Two studies of animal models reported that the use of stomach segments is a viable alternative and has functioned well, causing no gastrointestinal complications or genitourinary problems.[15, 16] Others, using a canine model, have shown that urine, or some component of urine, appears to suppress antral gastrin secretion as measured by serum gastrin concentrations and antral G cell hyperplasia.[7, 18] Lau *et al* showed that 4% aqueous peptone solution instilled into exteriorised antral pouches caused a significant increase in mean serum gastrin concentrations, compared with little or no change in mean serum gastrin with a 4% aqueous peptone solution in concentrated dog urine.[18] Muraishi *et al*, however, reported a markedly decreased postprandial urine pH (2·4–4·2) in six dogs undergoing gastrocystoplasty at six months' follow up.[19] More importantly they found that histological erosions developed in the bladder remnant in five dogs, and an ulcer in the native bladder remnant in the sixth dog. Tiffany *et al* reported severe hypergastrinaemia after the operation that led to the development of gastric ulcers in dogs undergoing gastrocystoplasty.[20] Renal function was not addressed in these studies.

Based on our findings for patients 2, 4, and 5 in our series, we believe that their native bladder epithelium lacked some form of cytoprotection against the normal acid production of the transplanted gastric segment. Cystoscopy in two of these patients showed haemorrhagic cystitis of the native bladder, but not of the transported gastric segment, probably the consequence of acidic urine.

Epidermal growth factor, or urogastrone, a normal constituent of canine and human urine, has been shown to inhibit gastric acid secretion after parenteral administration and is required for ongoing urinary tract epithelial growth. Horikoshi *et al* have shown that decreased production of epidermal growth factor and local differences of epidermal growth factor concentrations may be contributing factors to the development of dysplastic mesonephric tissue and also to normal urinary tract epithelialisation.[21] It may be important to ensure quality urine production before gastrocystoplasty to provide adequate epithelialisation of the neosegment from the surrounding native bladder epithelium and thus protect it from acid secretion. Inadequate amounts, low concentrations, or inactivation of growth factors, or lack of some other factors may have contributed to the bladder pathology.[22, 23] Lack of cytoprotection may explain why patients 2 and 4, who had comparable glomerular filtration rates, developed similar cystoscopic and clinical findings, compared with patient 1, who had a significantly better glomerular filtration rate and who developed none of the observed complications. Patient 5, however, was symptomatic and had clinical evidence of haemorrhagic cystitis and an acid urine pH early in the course of her treatment, despite a glomerular filtration rate similar to that of patient 1. The difference in quality of urine production in patients 1 and 5, resulting in one patient developing symptoms and the other not, may eventually be explained when the cytoprotection factors in urine can be evaluated.

Neutralisation of acid urine provided relief in all patients. Bladder irrigation with bicarbonate alleviated symptoms, but its effect was short lived and the procedure time consuming. Patients 2 and 4 had inadequate relief of symptoms with H_2 blockers and required treatment with omeprazole. Omeprazole is the first of a new class of drugs that inhibit gastric secretion by altering the activity of hydrogen/potassium ATPase.[24,25] This drug has been used in a variety of patients for whom hyperacidity is a major problem (for example, Zollinger-Ellison syndrome) and who have been refractory to more conventional H_2 blockers or antacids.[26]

Studies have implicated the long term use of omeprazole in gastric carcinoma in rats, secondary hypergastrinaemia, and hyperplasia of enterochromaffin cells.[24] In one study of the long term effects of gastrocystoplasty in rats,[27] follow up 18 months after the operation showed prominent histopathological changes of the bladder in the gastrocystoplasty group, ranging from atrophy of glands in the gastric patch, to tumours of the mucosal surface. Patients who are at risk for development of cancer because of immunosuppression after renal transplant may develop dysplastic changes in the bladder epithelium from long term exposure to an acid environment. We therefore believe that any patient undergoing gastrocystoplasty should be monitored with regular cystoscopy. Furthermore, these patients may also require long term treatment with omeprazole, which may further enhance their risk of developing a malignancy.

Patients with chronic renal failure may be at greater risk for gastrointestinal complications from gastrocystoplasty. Uraemia and chronic renal failure have often been reported as causes of gastrointestinal symptoms such as nausea, vomiting, anorexia, and poor weight gain. These symptoms may be aggravated by gastric surgery.[28]

Descriptions of the animal model of gastrocystoplasty report the surgical excision of only a small segment of stomach from the gastric antrum to form the augmented neobladder.[3] Too small a gastric flap often results in inadequate bladder augmentation. Conversely, the larger the gastric segment the greater the risk for developing gastrointestinal complications.[4 7 29] Therefore, patient size and age may be important factors in assessing suitability for this procedure.

Gastrectomy, which alters gastric motility and changes gastric compliance, probably resulted in the symptoms experienced by patients 1 and 3, namely, vomiting, dumping syndrome and food aversion,[30 31] nausea and early satiety, and failure to thrive. The dumping syndrome of patient 1 was eventually alleviated by the addition of medium chain triglyceride oil and cornstarch to Peptamen (Carnation) delivered through a nasogastric tube to delay gastric emptying.[13] The severe oesophagitis observed in patient 3 was probably avoided in patient 1 by the antireflux procedure (Nissen fundoplication) performed after the gastrocystoplasty. We are not, however, advocating this as a concurrent procedure in all patients undergoing gastrocystoplasty as Nissen fundoplication may be accompanied by complications such as rapid gastric emptying and dumping syndrome.[30] The food aversion of patient 3 was probably due to severe oesophagitis.[30 32] With conventional treatment (cisapride, ranitidine, and a high carbohydrate, low fat diet), we were able to alleviate his symptoms.

In summary, there are considerable gastrointestinal complications associated with gastrocystoplasty. As a result of the complications observed in all of our patients who have undergone gastrocystoplasty, we believe that the use of this procedure for bladder augmentation in infants and children, particularly those with chronic renal failure, warrants caution. Future research should focus on animals with previously induced chronic renal failure. Only after long term follow up and more extensive experience with gastrocystoplasty in children will we be able to evaluate the viability of gastrocystoplasty as an alternative to more conventional techniques for bladder augmentation.

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All Greek

Here's a fascinating fact for you. I bet you didn't know that Greek eggs contain eight or nine times as much docosahexaenoic acid (DHA) as standard American supermarket eggs (Artemis P Simopoulos and Norman Salem, Jr, *American Journal of Clinical Nutrition* 1992;55:411–4). But then, when the fatty acid has a name like that, they would, wouldn't they? And if the author's name had been Simopollochkov they'd probably have been Russian eggs.

Studies have shown that infant formulas are lacking in such long chain polyunsaturated fatty acids which are present in human milk. DHA may be an essential nutrient as there is evidence that babies who don't get enough of it have deficient functioning of the retinal rods. Eggs are used as a source of fatty acids for infant formulas but their content of DHA varies according to how the hens were fed. American supermarket eggs were found to have a low content, eggs from hens fed on flax or on fishmeal contained more, but free range (Greek) eggs contained most of all. Other studies have shown that in plants, eggs, fish, and meat the wild or free varieties have a greater content of certain fatty acids than the cultivated or restrained. So that's another one up for the Greens. Infant feeding is so complex it's a wonder that any of us grow up to have an ounce of sense or even grow up at all (see Archivist 1991:1290).

ARCHIVIST

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Prepubertal height velocity references over a wide age range

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Abstract

In order to correct height velocities for the confounders age and sex, SD scores can be calculated using the mean and the SD of the height velocity in the normal population. However, current methods are inappropriate for prepubertal children in the age range in which puberty occurs, because reference groups then consist of a mixed prepubertal/pubertal population. The mathematical infancy-childhood-puberty (ICP) model opens up the possibility of dissecting the puberty component from the total growth curve. New references for height velocity for prepubertal children calculated over a 12 month interval up to the ages of 15·5 years (boys) and 13·5 years (girls) have been constructed on the basis of adaptations of the ICP model and the Swedish longitudinal growth study.

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In the evaluation of growth disorders, height velocity is one of the main parameters by which we recognise abnormal growth and judge the impact of therapeutic intervention. When groups of patients are studied, height velocity is usually expressed as SD score to remove the influences of age and sex. However, there is a serious methodological problem in using height velocity SD score for prepubertal children after the age at which children can start puberty. The reference population then consists of a changing mixture of prepubertal and pubertal children so that the mean height velocity of the whole cohort does not represent the mean of the prepubertal children. This also leads to a non-Gaussian distribution. Therefore, mean and SD values for prepubertal children have been reported only up to the age of 8·75 years (boys) and 6·75 years (girls).[1]

To extend the age range, the best solution would be to measure height velocities in a large group of prepubertal, healthy, but relatively late maturing adolescents. However, no such data are available. To overcome this problem, in British studies the 50th centile from the whole cohort is used as mean and a hypothetical fixed SD (identical to the SD in late prepubertal years) is taken until the end of growth (CGD Brook and PC Hindmarsh, personal communication).[2] However, the mixed prepubertal/pubertal reference population gives an overestimation of the mean height velocity for prepubertal children. Others, including ourselves, have used height velocity SD scores for bone age by substituting bone age for chronological age, assuming that the mean height velocity for bone age in the population equals the height velocity for chronological age.[3] This assumption is theoretically plausible for healthy children with an average bone maturation, but becomes unlikely for children with an extreme delay or advance of bone age. For example, in children with a delayed bone age the height velocity SD score for bone age is lower than the height velocity SD score for chronological age, due to the downward slope of the mean height velocity curve. Furthermore, no data are available about the SD values for height velocity for bone age.

In this paper we present a new method of obtaining age references for height velocity during the whole period in which healthy children can remain prepubertal.

Methods

As basis for our model we adapted the infancy-childhood-puberty (ICP) model.[4] The reason for using this model is that it explicitly divides the total growth curve in a prepubertal and pubertal section. However, there are two disadvantages to using the ICP model in its present form as a reference model for height velocity. Firstly, the prepubertal growth curve is composed of two components (the infancy and childhood component), of which the childhood component is supposed to start between 6 and 12 months at a mean age of 9 months. Due to the abrupt introduction of this childhood component there is a sudden increase in mean height velocity at 9 months, which for individual patients with a mean onset of this component may be true but not for the whole reference population. Secondly, from 0–2 years of age the mean and SD of height velocity are presented over intervals of three and six months and thereafter over intervals of 12 months, while it is known that the SD correlates inversely with the length of the interval.[5]

To correct for these problems we adapted this ICP model using the data from the Swedish longitudinal growth study.[6] The reason for using the Swedish growth study is that it is based on a relatively large sample and that the growth pattern of Swedish children in the 1960s is similar to the present growth of children in many northern European and North American populations.[5 7–10]

The first problem of the ICP model was solved by smoothing the transition from the infancy to the childhood component by interpositioning a second degree polynoma between the ages of 0·5 and 3·0 years. This polynoma had to meet the following requirements:

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- At $t=0·50$ it should connect exactly to the infancy component
- At $t=1·75$ it should be identical to the observed height velocity in the Swedish population
- At $t=3·00$ it should connect to the combined infancy+childhood component.

The second problem was approached by recalculating the whole year SDs in the first and second year (J Karlberg, personal communication). With these data and the other Swedish prepubertal SD data (boys<10 year, girls<8 years), we constructed the best fitting curve, on the basis of the original equation from the ICP model, which is an exponential curve ($a+e^{(-b \cdot t+c)}$). Because no data are available of the SD of prepubertal children during the years that some children from the reference population enter puberty, we extrapolated the SD after the ages of 10 (boys) and 8 (girls) years.

The ages of 15·5 years (boys) and 13·5 years (girls) were taken as upper limits because a prepubertal stage beyond these ages is assumed to be non-physiological. The computer program EnzFitter version 1·05 (Elsevier Biosoft, Cambridge) was used to calculate the parameters for the curves.

Results

The equations for the mean height velocity at 0·5–3·0 years (the interposition between the infancy and childhood component), and at ages above 3·0 years (childhood component) are shown in table 1. Figure 1 shows the mean height velocity curves from the original ICP model and the interpositioned polynoma for boys. Figure 2 shows the model for boys in relation to the Swedish[6] and the British[1] references and to the American references of late maturers.[5]

The equation for SD versus age is shown in

Table 1 Equations for mean height velocity (HV) on age t

$t \geq 0·5$ and $\leq 3·0$ years. $HV_I(t)=a_I+b_I\,t+c_I.t^2$	*Boys*	*Girls*
a_I	27·11	25·28
b_I:	−12·73	−11·07
c_I	2·06	1·73
$t \geq 3·0$ years: $HV_c(t)=b_c+c_c\,t$	*Boys*	*Girls*
b_c	8·54	8·83
c_c:	−0·18	−0·21

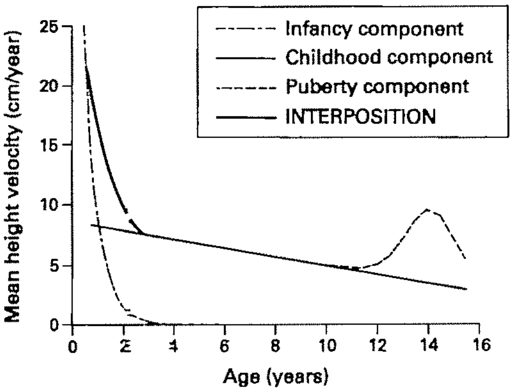

Figure 1 The original ICP model describing height velocity and our adaptation. The IPC Growth Standard: Copyright c 1987 J Karlberg ISBN 91-7900-265-X, and Copyright c in the US 1989 J Karlberg TX 2560 182; published with permission

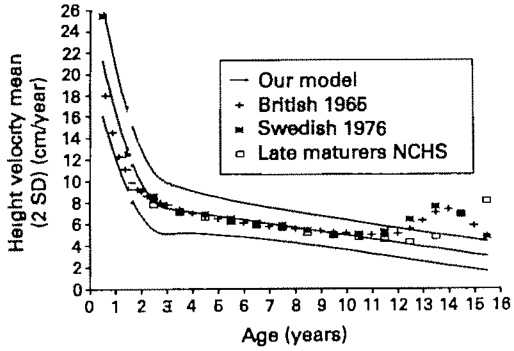

Figure 2 Height velocity (±2 SD) according to our model in relation to other references (boys).

Table 2 Equations for SD of height velocity on age t

$HVSD_R(t)=a_R+e^{-b_R\,t+c_R}$	*Boys*	*Girls*
a_R:	0·691	0·820
b_R:	0·538	0·649
c_R:	0·912	0·635

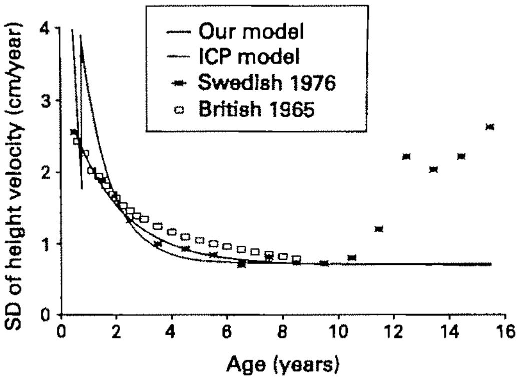

Figure 3 SD of our model compared with other references (boys). The IPC Growth Standard: Copyright c 1987 J Karlberg ISBN 91-7900-265-X, and Copyright c in the US 1989. J Karlberg TX 2560 182; published with permission.

Table 3 Reference data for whole year height velocities for prepubertal children using the new equations

	Boys		*Girls*	
Age	*Mean*	*SD*	*Mean*	*SD*
0·5	21·26	2·59	20·18	2·18
1·0	16·44	2·14	15·94	1·81
1·5	12·65	1·80	12·57	1·53
2·0	9·89	1·54	10·06	1·34
2·5	8·16	1·34	8·42	1·19
3·0	7·46	1·19	7·64	1·09
3·5	7·28	1·07	7·41	1·01
4·0	7·10	0·98	7·20	0·96
4·5	6·92	0·91	6·99	0·92
5·0	6·74	0·86	6·78	0·89
5·5	6·56	0·82	6·57	0·87
6·0	6·38	0·79	6·36	0·86
6·5	6·20	0·77	6·15	0·85
7·0	6·02	0·75	5·94	0·84
7·5	5·84	0·74	5·73	0·83
8·0	5·66	0·72	5·52	0·83
8·5	5·48	0·72	5·31	0·83
9·0	5·30	0·71	5·10	0·83
9·5	5·12	0·71	4·89	0·82
10·0	4·94	0·70	4·68	0·82
10·5	4·76	0·70	4·47	0·82
11·0	4·58	0·70	4·26	0·82
11·5	4·40	0·70	4·05	0·82
12·0	4·22	0·69	3·84	0·82
12·5	4·04	0·69	3·63	0·82
13·0	3·86	0·69	3·42	0·82
13·5	3·68	0·69	3·21	0·82
14·0	3·50	0·69		
14·5	3·32	0·69		
15·0	3·14	0·69		
15·5	2·96	0·69		

table 2. The SD from our model together with Swedish and British data is illustrated in fig 3. The calculated mean and SD values over the whole prepubertal period are shown in table 3.

Discussion

Height velocity is commonly used as a sensitive short term parameter for assessing growth and growth intervention. One of the criteria used for the diagnosis of growth hormone deficiency is a height velocity less than the 25th centile.[11] Although height velocity is not very stable over time,[12] a positive change in height velocity is generally considered as a good response to growth promoting treatment.[13 14]

In growth studies in groups of prepubertal children within a wide age range, the use of height velocity expressed in cm/year is not suitable because of the large confounding effect of age and to a lesser extent, sex. The usual method to overcome this problem, the use of SD scores on the basis of longitudinal growth studies, is only possible for young children. Later on, the pubertal growth spurt, which starts at a variable age, complicates the situation in two ways. First, no reference group consisting of only prepubertal children is available. Second, the variation in the timing of puberty and the great changes in height velocity during puberty destroy the Gaussian distribution.[1] Because of the drawbacks of the methods currently used to overcome this problem, we searched for a better one.

The ICP model is a mathematical model in which total statural growth is described by a superposition of three equations.[15] It has been hypothesised that the first and second component would be associated with distinct ways of biological regulation,[16 17] in the sense that the infant component would not be growth hormone dependent. On the basis of our and other observations, this is unlikely.[18] We therefore felt that there would be no biological reasons to abstain from smoothing the transition between the infancy and childhood components. However, there is little doubt that the pubertal growth spurt is under the influence of other factors, notably sex steroids.

In contrast to the first report on the Swedish longitudinal study[6] and the description of the data on the basis of the ICP model,[4] we decided to use only growth velocity data over one year intervals between 1 and 24 months of age, rather than over two, three, and six months. This has no great influence on the mean height velocity, while it reduces the size of the SD, which is much larger over shorter intervals. This implies that our model may only be applied on velocities that are measured over 12 months. It can be argued that during infancy the growth velocity is so high and changes so rapidly, that calculating velocity over a period of a year is too insensitive as a parameter of growth. However, the use of a shorter period in infancy would automatically give rise to the dilemma to choose the age from which the period should be increased to a year, and this woud obviously cause a disruption in the curve of the SD score by age.

Another difference with the original ICP model is that we smoothed the height velocity curve in the second semester by the interposition of a polynoma. This smoothing procedure was necessary for two reasons. First, the use of yearly growth velocities over the whole growth period implied that the sudden acceleration observed by Karlberg[4] between 6 and 12 months of age would disappear anyhow. Second, the presence of a sharp angle in the curve of the mean growth velocity would lead to methodological artefacts in calculating SD scores.

It is common practice to transform a height velocity always to cm/year, even when it is measured over a shorter interval than a year. The question is whether such growth velocity could be transformed to SD scores and, if so, which reference data should be used. It should be emphasised that, due to the relatively large measurement error, comparison of velocities measured over unequal intervals is theoretically incorrect. However, if by circumstances no yearly velocities are available, the SD score should be calculated using a higher SD than provided by our model. SD values over two and three month intervals in the first year of life and over six months intervals in the second year have been provided by the Swedish investigators and are indicated in fig 3.[4] However, exact data on the size of the SD for various intervals at various ages are unavailable, which increases the unreliability of SD scores over short periods.

While our model lacks most of the drawbacks of alternative methods, it should be emphasised that it is based on unproved assumptions with respect to the age references for prepubertal teenagers, as both mean and SD in this age period are obtained by extrapolation. To test the validity of our model, large data sets from late maturing adolescents are needed, which until now are unavailable.

We thank Dr Herman Wijnne for the aid on the mathematical part of the study and Dr Bart Boersma for critical reviewing the manuscript

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Commentary

Growth and puberty are intimately related and in the adolescent age range it is difficult to dissociate one from the other. There are several variable factors affecting growth at adolescence. Normal children enter puberty at differing ages, from 9·0 to 13·5 years in girls and from 9·5 to 14·0 years in boys. They also progress through puberty at differing rates; the fastest girls pass through puberty in 18 months whereas the slowest boys may take five years. In younger children (<8 years in girls and <9 years in boys) it is acceptable practice to use SD scores to compare a child's height with the height of normal children of the same chronological age. Unlike growth in younger children, growth standards for a whole population during the pubertal years have little meaning when applied to an individual; it depends on what stage of puberty an adolescent has attained. Therefore in the adolescent years, it is more appropriate to compare rate of growth with children of the same stage of sexual maturation than those of the same chronological age.

Clinicians are often presented with the problem of a child with late puberty and attempt to relate growth rate to chronological age by experience of what is perceived to be normal: is the problem abnormal growth or abnormal puberty? This is an important distinction to make in order to reduce the number of inappropriate endocrine investigations and to limit the use of growth hormone treatment to those who would benefit. This is of particular relevance in this clinical situation as all tests of growth hormone secretion are notoriously difficult to interpret in the phase of growth deceleration of late prepuberty in boys and girls and early puberty in boys. The authors present data that provide a continuum of growth standards throughout prepuberty, so that a meaningful height SD score can be calculated, despite many children being less advanced in sexual maturation than their peer group. Paediatric endocrinologists usually extrapolate normal data for growth velocity in children with absent puberty in a similar fashion to the data in figs 1 and 2. However Rikken and Wit have been able to quantify this which is a step forward in providing height SD score data with which to determine if growth is abnormal, even in the absence of pubertal development.

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Bone age, social deprivation, and single parent families

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Abstract

It is well known that deprivation affects bone growth. The study was set up to investigate what aspects of deprivation are of greatest importance. Bone ages of 1593 child trauma patients aged 0–19 years from Middlesbrough General Hospital, Cleveland, were related to local authority ward indices of socioeconomic status (51 wards). After adjustment for chronological age and sex, the mean bone ages in each ward were highly significantly negatively associated with five ward indices of deprivation: the rate of single parent families, low car ownership, unemployment, rented housing, and overcrowding. There was a mean four month deficit in bone age among children living in wards with the highest single parent family rates. The inverse association between deprivation and bone age is unlikely to be causal throughout childhood, as older and younger children were affected to the same extent. However the bone age deficit could be caused by deprivation retarding skeletal maturation during a critical period in early life.

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There is considerable evidence that adverse socioeconomic circumstances affect the rate of skeletal maturation, although the mechanisms involved are not clear. Differences in skeletal maturity have been observed among children differing in a variety of ways including geography, income, nutrition, home conditions, and psychosocial factors.[1–9] However the compared groups have tended to be relatively disparate, in terms either of clinical status or geography, and it is not clear to what extent, within the community, deprivation affects skeletal maturity.

Recent work has shown that poor perinatal growth is a risk factor for ischaemic heart disease, stroke, and obstructive lung disease in later life.[10] This has been proposed as an example of programming, where circumstances at a critical period in early life dictate the individual's future health status. The present study, covering a small geographic area of Britain, was carried out using radiographs of trauma patients to investigate in more detail the link between skeletal maturity, as measured by Greulich-Pyle bone age, and indices of socioeconomic status. The aim was to find out which indices were most closely associated with skeletal retardation, and to identify at what ages the association was strongest.

Subjects and methods

Some 2000 packets of *x* ray films, belong to patients who had had hand radiographs for trauma when under the age of 20 years, were retrieved from the archives of Middlesbrough General Hospital, Cleveland. Most patients had been radiographed during the years 1979–81. Over 300 records were discarded, because either all the epiphyses had fused, or the radiographs were missing, technically inadequate or illegible, or the patient did not reside within the boroughs of Middlesbrough or Langbaurgh.

The bone ages were estimated blind by AJLC using the atlas of Greulich and Pyle.[11] In a minority of cases where the bone age lay between two adjacent standards, the mid-age was used. The subject's identifying number, sex, date of birth and examination, bone age, and local authority ward from their address were then recorded. Race was not recorded, but the subjects were probably almost all white; the population of Cleveland is only about 3% non-white, and of this only a small fraction is Afro-Caribbean.

The subjects came from 51 distinct local authority wards. Information on 13 socioeconomic indices for each ward from the 1981 census was obtained, expressed per 1000 households or population as appropriate (see list in table 4).

STATISTICAL METHODS

The data were scrutinised for anomalies between bone age and chronological age, and patients who had been referred for poor growth rather than trauma were excluded. In addition erroneous dates of birth and examination were corrected.

Multiple regression analysis was used to relate each subject's bone age to chronological age, sex, and the subject's socioeconomic information as obtained from their ward. The chronological age adjustment was done using a polynomial in age. An overall sex effect and interactions of sex with each term of the fitted polynomial were also included. This is equivalent to fitting separate polynomials for the two sexes.

Regression was used to compare the ability of the different ward socioeconomic indices to explain the residual variation in bone age, after adjusting for chronological age and sex. The significance of each ward index was assessed relative to the between ward variation, so that the *t* statistic for the significance of the index was given by

$$t=\sqrt{49\,R^2/(1-R^2)},$$

with 49 residual degrees of freedom, where R was the weighted correlation, across wards, between the mean adjusted bone age and the socioeconomic index, the weightings corresponding to the numbers of subjects in each ward.

Results

A total of 1683 radiographs from 1593 subjects were available for analysis. Eighty four subjects had more than one radiograph: 80 with two, three with three, and one with five. All such radiographs except the first were excluded from the analysis, leaving a total of 1593. The age and sex distribution of the sample is given in table 1. The sex ratio was 63:37, and the modal ages for boys and girls were 14 and 11 years respectively, with a sharp increase in numbers from age 11. The subjects came from 51 distinct local authority wards, with a median number of 29 subjects per ward (lower and upper quartiles 20 and 39; range 6–94).

Scatterplots of bone age versus chronological age are shown in figs 1 and 2 for boys and girls, with fitted cubic polynomials in chronological age superimposed. Table 2 gives the regression equations for the polynomials, and also for a simpler linear model containing just age and sex. The linear model shows that, after adjusting for chronological age, mean bone age is 0·27 years greater in the girls than in the boys, and that the age regression coefficient of 0·951 is highly significantly less than 1 ($t=-7\cdot1$, $p<<0\cdot001$).

Table 3 summarises the analysis of variance of bone age after fitting polynomials of increasing degree for the two sexes up to fifth order.

Table 1 Age and sex distribution of subjects studied

Age (years)	*Boys*	*Girls*	*Total*
0+	9	4	13
1+	20	13	33
2+	21	23	44
3+	27	18	45
4+	23	23	46
5+	14	17	31
6+	30	19	49
7+	33	21	54
8+	45	25	70
9+	40	38	78
10+	50	34	84
11+	73	81	154
12+	91	67	158
13+	105	54	159
14+	128	59	187
15+	105	44	149
16+	84	27	111
17+	75	7	82
18+	45	1	45
Total	1018	575	1593

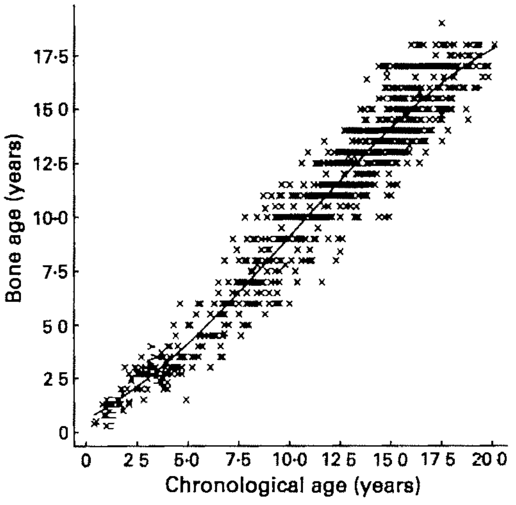

Figure 1 Scatter diagram of Greulich-Pyle bone age versus chronological age in 1018 boys, with the fitted cubic in chronological age.

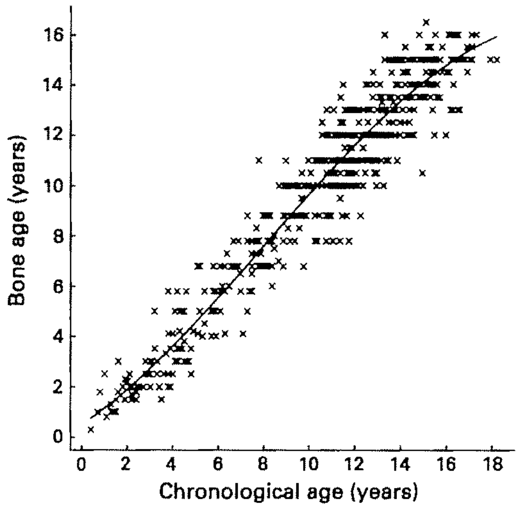

Figure 2 Scatter diagram of Greulich-Pyle bone age versus chronological age in 575 girls, with the fitted cubic in chronological age.

Table 3 The analysis of variance table from the regression of bone age on chronological age polynomials of increasing order. Terms such as Age.Sex indicate the interaction of age and sex, that is the difference between sexes in the age term

Term	*Degrees of freedom*	*Sum of squares*	*Mean square*	*Variance ratio*
Age	1	27342·84	27342 84	19897 94***
Sex	1	25·27	25 27	18 39***
Age Sex	1	1·70	1·70	1·24
Age^2	1	7·17	7·17	5 22*
Age^2 Sex	1	5·72	5 72	4 16*
Age^3	1	56 59	56 59	41 18***
Age^3.Sex	1	0 15	0·15	0 11
Age^4	1	1 11	1·11	0·81
Age^4.Sex	1	0·56	0 56	0·41
Age^5	1	10·81	10 81	7 86**
Age^5.Sex	1	3·15	3 15	2 29
Residual	1581	2172·54	1 37	
Total	1592	29627·61	18 61	

$^{*}p<0\cdot05$; $^{**}p<0\cdot01$; $^{***}p<0\cdot001$

Table 2 Regression models of bone age on chronological age and sex. Results are given as regression coefficient (SE) for each term. The linear model is for the two sexes combined

Model	*Constant*	*Female sex*	*Age*	*(Age-12)^2*	*(Age-12)^3*
Linear	−0·307 (0·093)	0·266 (0·063)	0 951 (0 007)	—	—
Cubic for boys	−1·164 (0·214)	—	1·029 (0·017)	−0 0102 (0 0023)	−0·00189 (0 00034)
Cubic for girls	0·324 (0 272)	—	0 936 (0 022)	−0 0243 (0·0056)	−0·00213 (0·00064)

This table shows the significance of each extra term as the order increases, with the linear term being massively significant and accounting for over 92% of the variation. The cubic terms and quintic terms are also highly significant ($p<0\cdot01$), but they account for only a small proportion of the total variation. There is also a highly significant difference in mean bone age between the sexes, but the only significant age-sex interaction is the quadratic term ($p<0\cdot05$).

After adjusting for sex and age using the sex specific cubic polynomials, the mean adjusted bone ages for each ward were significantly different from each other ($F=1\cdot48$ on 50 and 1535 df, $p=0\cdot02$), with a range in mean bone age of 1·23 years. Table 4 summarises the ability of each of the 13 socioeconomic indices to explain the ward differences in bone age. Five of the 13 indices are highly significant, and the rate of single parent households in each ward is the best predictor ($r=-0\cdot49$, regression coefficient $-0\cdot00086$, $p=0\cdot0003$). Car ownership, unemployment, rented housing, and overcrowding are also highly significant, but become insignificant after adjusting for the single parent household rate. Three of the other insignificant indices relate to the numbers of old people in each ward.

Figure 3 shows the plot of mean adjusted bone age for each ward plotted against the corresponding single parent household rate, with the fitted regression line superimposed. The size of each point reflects the number of subjects in the ward. The difference in mean adjusted bone age between wards with low (10 per 1000) and high (50 per 1000) single parent household rates is 0·34 years, or four months.

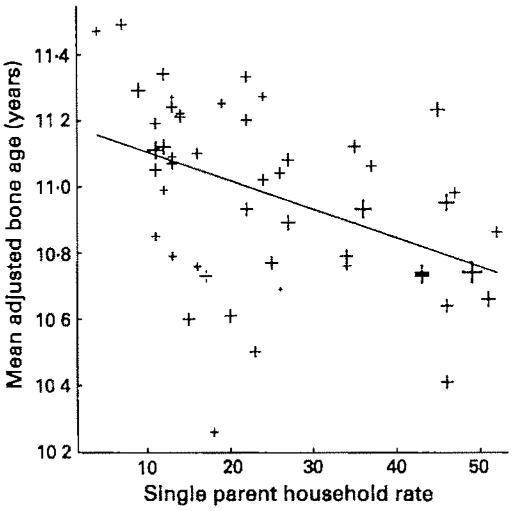

Figure 3 Scatter diagram of mean adjusted bone age versus the rate of single parent households in 51 local authority wards, with the fitted regression line. The size of each point is proportional to the number of subjects in that ward.

Table 4 The relative importance of 13 socioeconomic indices for explaining the difference in bone age between wards, after adjustment for chronological age and sex. Data are the correlations and regression coefficients of mean adjusted bone age on each index in turn, weighted according to the numbers of subjects in each ward. Each regression coefficient shows the effect on a ward's mean adjusted bone age, in years, of a unit change in the index

Socioeconomic index (per 1000)	*Correlation*	*Regression coefficient*	*Significance level*
Households with one parent	−0·49	−0·00858	0·0003
Households with no car	−0·46	−0·00055	0·0008
Unemployed males 16–64 years	−0·45	−0·00119	0·0008
Households in rented housing	−0·43	−0·00036	0·002
Households with more than one person/room	−0·42	−0·00324	0·002
Households with three or more dependent children	−0·34	−0·00314	0·02
Children under 5 years	−0·25	−0·00366	0·08
Households of a pensioner alone	−0·24	−0·00167	0·09
Households with pensioners only	−0·11	−0·00054	0·5
Adults over 74 years	−0·09	−0·00156	0·6
Head of household born in New Commonwealth	−0·08	−0·00045	0·6
Households sharing/lacking a bath	−0·07	−0·00069	0·7
Households in multioccupied dwellings	0·03	0·00062	0·9

Importantly, there is no evidence that the effect of the single parent index on bone age varies by age or sex (t values for interaction terms of single parent index with age and sex 0·66 and 0·92 respectively, $p>0\cdot3$). Thus the effect is the same at all ages.

Discussion

The study has demonstrated a highly significant negative association between the skeletal maturity of children radiographed for trauma and indices of socioeconomic status in the wards where they live. The best single predictor is the ward rate of single parent households, but other highly significant indices are low car ownership, unemployment, rented housing, and overcrowding.

Two factors relating to the study's validity need to be considered: (i) how valid Greulich-Pyle bone age is for measuring skeletal maturation and (ii) how representative trauma patients age of the population of Cleveland children. The method of Tanner and Whitehouse (TW2)[12] has been advocated for the estimation of bone age[13] rather than Greulich-Pyle, because it is claimed to be more accurate. The greater time and effort required by the TW2 method is cited as being more than offset by its greater accuracy and precision. However the authors have found previously that Greulich-Pyle, although providing an underestimate of chronological age, is at least as consistent as TW2, with lower inter-observer variation.[14] Other workers have reached similar conclusions, and have advocated the Greulich and Pyle method for population based studies of skeletal age.[1 15 16] In this study the inherent under estimation of the method is adjusted for by regression analysis, and the absolute bone age is of less importance than the discrepancy between chronological and bone age.

The slope of the regression line relating bone age to chronological age in the present study is 0·951 with a SE of 0·007 (table 3), very similar to the study of Cole *et al* where the regression coefficient was 0·939 (SE 0·031).[14] There is also no evidence that the age coefficient differs between the sexes (table 3), and the sex specific cubic curves are very similar in shape (figs 1 and 2). More curious is the highly significant difference in mean adjusted bone age between the sexes (table 2), with the girls 0·27 years older than the boys. This implies that compared with children in the original Brush Foundation sample,[11] Cleveland girls are relatively more advanced than Cleveland boys. Why this should be is not obvious, although two other surveys have seen the same sex effect.[1] It may mean that boys are more fragile than girls in the face of deprivation, but alternatively and perhaps more convincingly, the Brush Foundation's strict selection criteria may have introduced a sex bias in the reference data.

The present study sample, children brought to hospital for trauma, is clearly not a random sample of Cleveland children. For a start its age distribution is weighted towards the teenage years, and boys are over represented (table 1). It is also likely to be weighted towards children living nearer to Middlesbrough General Hospital. Nevertheless these and other possible biases can only affect the validity of the observed association to the extent that they might actually generate it. For this to happen, children from the more deprived wards would need to be more likely to attend hospital for trauma if they were skeletally immature, whereas in the well off wards the bias would need to operate the other way. This, though possible, is unlikely. One other possibility, that the reading of the radiographs was biased, can be ruled out as they were read blind.

Thus the association between skeletal maturity and socioeconomic status is likely to be valid. An association in this detail has not previously been demonstrated, and the obvious question is: Is it causal? The possible alternatives are that reduced maturation leads to deprivation (which is not feasible), or that deprivation causes reduced maturation, or that both deprivation and reduced maturation are caused by some other common factor.

Rona and Chinn showed an association of height in childhood with deprivation, which they argued arises from a period in early life when deprivation causes growth faltering.[17] They found that after adjusting for father's social class, parental height, family size and child's birth weight, primary schoolchildren of unemployed fathers were shorter than children whose fathers were employed. However when they looked at height gain over two years there was no longer an association with unemployment. This could be explained by unemployment having a causal effect on height growth earlier in life,[18] but not later, so that the deficit seen at school age dates back to the preschool period.

In the present study the linear relationship between bone age and chronological age is shifted downwards in the presence of deprivation, that is the constant term (intercept) is reduced. However there is no evidence that the *slope* of the line is affected by deprivation, so that children from all wards, whatever their socioeconomic status, track along lines of the same slope. This pattern can be explained by arguing that, just as for height growth, deprivation has a causal negative influence on bone age early in life, but that thereafter it has no effect. Thus young children from the more deprived wards become skeletally retarded compared with well off children, but once they are past the vulnerable period they mature at the same rate as everybody else, so that their bone age deficit remains the same throughout the growth period.

This explanation presupposes that each ward has a level of deprivation associated with it which determines the amount of retardation that infants living there are likely to experience. The causal relationship, if it exists, is thus between the deprivation of the ward and the retardation of infants living there. In practice one cannot measure the *actual* level of deprivation that each child experienced as an infant, partly because the avaliable indices were for 1981, a time when most of the sample were no longer infants. But in addition a substantial proportion of them would have moved house since infancy, so that their current address would be of even less relevance.

For these reasons each child's current address has to be viewed as a proxy for their address, and hence their degree of deprivation, in infancy. It is reasonable to assume that on average, relative deprivation does not change as children grow up, whether or not they move house. Children living in the same area ought to have experienced the same level of deprivation in infancy whether or not they are born locally. Thus the argument for causality is an indirect one, that current ward deprivation acts as a proxy for deprivation in infancy, and it is this which causally affects skeletal maturation.

The alternative explanation for the observed association is that both bone age deficit and deprivation are mediated by a third, probably genetic factor. However Rona and Chinn showed that genes fail to explain the height-unemployment link, as it survives adjustment for parental height and child birth weight.[17] Part of the height deficit in the children of unemployed parents is likely to be due to skeletal retardation, so that this also appears to survive adjustment for genetic factors. Thus a genetic explanation for the link is unlikely.

If deprivation is the causal agent, then the indices of deprivation found to be significant here, that is single parent, low car ownership, unemployment, rented housing and overcrowding, must be proxies for factors affecting the growth of young children. The indices all represent poverty in some sense, but it is striking that the most significant of them, the rate of single parent families, is the only one that relates directly to child care. Thus the study provides evidence to support the hypothesis that deprivation in early life leads to skeletal retardation, and furthermore it highlights single parent families as being particularly at risk. This fits in with the concept of a critical period in infancy when adverse conditions have long term consequences on health, suggesting that deprivation at this time is of fundamental importance.[10]

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Ciprofloxacin toxicity

Ciprofloxacin is a fluoroquinolone antibiotic which is active against Gram positive and Gram negative bacteria, including *Pseudomonas aeruginosa*, and aminoglycoside and cephalosporin resistant enterobacteriaciae, chlamydiae, and rickettsiae. Because it has been shown to be toxic to joint cartilage in some growing animals its use in children has been frowned upon. The *British National Formulary* (September 1991) says that it is not recommended in children or growing adolescents but gives dosage recommendations for children for use 'where benefit outweighs risk'. It has been used in children to treat pseudomonal infection in cystic fibrosis and most of the adverse effects so far reported seem to have been in this context. A 16 year old girl developed swollen knees[1] and a 14 year old, benign intracranial hypertension.[2] Interstitial nephritis was reported in a small series of cystic fibrosis patients in Seattle, Washington.[3] An 11 year old boy, who did not have cystic fibrosis, was treated for typhoid fever and developed interstitial nephritis with acute renal failure.[4]

Because of its antibacterial spectrum, and in particular its activity against pseudomonas and against coliform organisms resistant to other antibiotics, the use of ciprofloxacin in the newborn may be attractive. A report from Thailand (Pagarkrong Lumbiganon and colleagues, *Pediatric Infectious Disease Journal* 1991;**10**: 619–20) records its use during an outbreak of severe neonatal klebsiella infection. Thirteen babies were treated; three died during the acute illness and two died later from other causes. Five of the remaining eight children were seen at between 12 and 23 months of age and two had greenish discoloration of the teeth. They had both been given many other drugs but none known to discolour the teeth.

The association is suggestive but does not prove that ciprofloxacin was responsible. It was tooth discoloration, of course, which put paid to the use of tetracyclines in children. The drug might still have a place in paediatric therapeutics when resistance to other antibiotics is a problem but clearly its use should be carefully monitored until we have a better idea of its risks.

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Centiles for adult head circumference

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Abstract

Reference range for head circumference on the Tanner charts do not go beyond age 16. In this study the head circumference and heights of 354 adults in two British centres were measured. The centile charts constructed from these measurements show that adult head circumference is related to height. The mean head circumference of a male of average height is above the 97th centile for a 16 year old on the Tanner charts. The paediatric charts are therefore inappropriate for use in adult males.

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Measurement of the occipitofrontal head circumference is an integral part of most paediatric and many medical examinations. It is often of particular importance in making a diagnosis in the dysmorphic child with developmental delay. The London dysmorphology database lists 250 syndromes associated with microcephaly and 114 with macrocephaly.[1] Many of these conditions are inherited and therefore accurate assessment and counselling of relatives should include measurement of head circumference. In the investigation of a child with an apparently isolated abnormality of head circumference examination should also include parental head circumference as studies have shown that up to 50% of normal variation in head size is familial.[2] The centile charts used routinely in Britain have data only up to age 16 years.[3] We have produced centile charts appropriate for use in adults.

Data collection

Data were collected on the head circumference, height, and age of 354 white adult volunteers attending the outpatient clinics of dental hospitals in Newcastle upon Tyne and Cardiff. Care was taken to exclude patients attending for conditions that might affect cranial anatomy. Two hundred and seven patients were measured in Newcastle (93 males and 114 females) and 147 in Cardiff (66 males and 81 females). The median age was 40 years (range 17 to 83). The subjects in Cardiff were measured by a single observer, whereas in Newcastle two observers measured approximately equal numbers.

Analysis

The approach was guided by the assumption that the head circumferences are normally distributed, a feature which was checked in the course of the analysis. Under this assumption the centiles were set using estimates of the mean and SD. So, for example, the 97th centile was calculated to be mean +1·88×SD. A further concern was that the mean and SD might depend on various recorded variables such as age and height. Thus the method for the simultaneous modelling of means and variances described by Aitkin was used.[4]

The use of this methodology also enabled a check to be made for evidence of a systematic effect of the centre (or observer) on the means (a bias) or on the variance (different precisions).

Results

Following Aitkin's recommendation a model was assumed for the means which allowed for all the factors mentioned above and some of their second order interactions and different models for the variance were considered.[4] There was no evidence that age, height, or sex had any effect

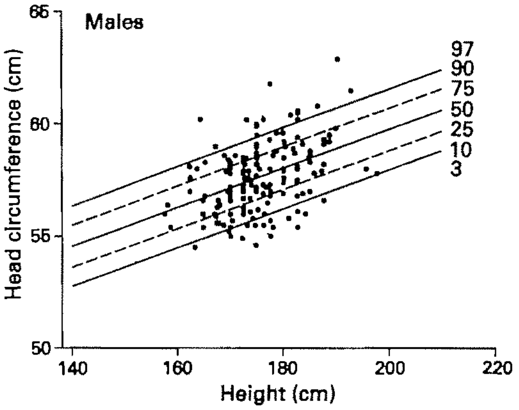

Figure 1 Head circumference plotted against height in 159 adult males. The line describing the mean of the distribution is 42·4+0·08673×height.

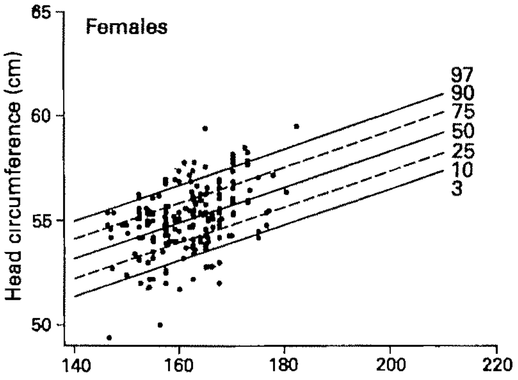

Figure 2 Head circumference plotted against height in 195 adult females. The line describing the mean of the distribution is 41·02+0·08673×height.

on the spread of the measurements. Moreover, there was no indication that the different observers had different precisions. (In a small sample, 20 subjects were measured twice: the SD of the intraobserver measurement error was 0·133 cm.)

As there was no need to include any variables in the model for the variance, Aitkin's approach reduces to ordinary multiple regression,[4] which was then used to examine the effect of age, height, and centre on the mean head circumference. No evidence was found of any effect of age nor of centre.

Figures 1 and 2 shows the data collected with the calculated centiles for males and females. There was clear evidence that mean head circumference increased with increasing height (slope 0·08673 cm/cm, SE 0·01031 cm/cm, $p<0·0001$) and that a male would have a head circumference that was on average 1·38 cm larger than that of a female of equal height (mean difference 1·378 cm, SE 0·211 cm, $p<0·0001$).

The relations given in the figures are reasonable for heights between 140 and 190 cm (females) and 150 to 200 cm (males). The SD about the line is 1·41 cm.

The centiles were constructed assuming the normality of the head circumference measurements, and this was confirmed by the normal probability plot of the jack-knife residuals. The Shapiro-Wilk test[5] did not discredit the hypothesis of normality ($W=0·986$, $p=0·69$, using Royston's approximation[6]).

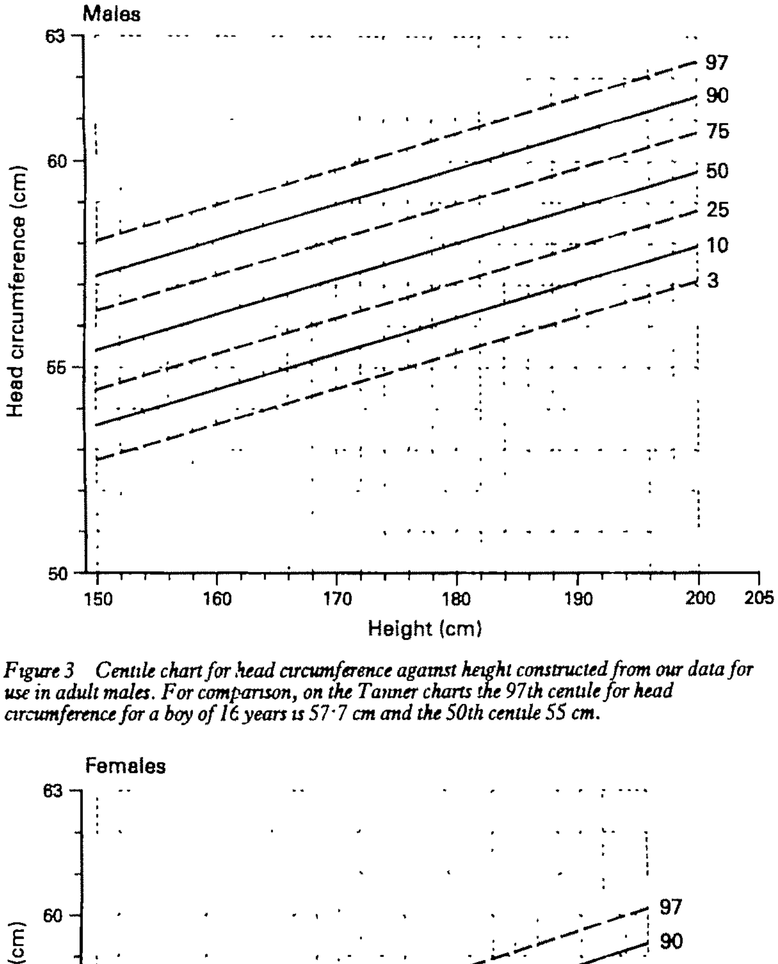

Figure 3 Centile chart for head circumference against height constructed from our data for use in adult males. For comparison, on the Tanner charts the 97th centile for head circumference for a boy of 16 years is 57·7 cm and the 50th centile 55 cm.

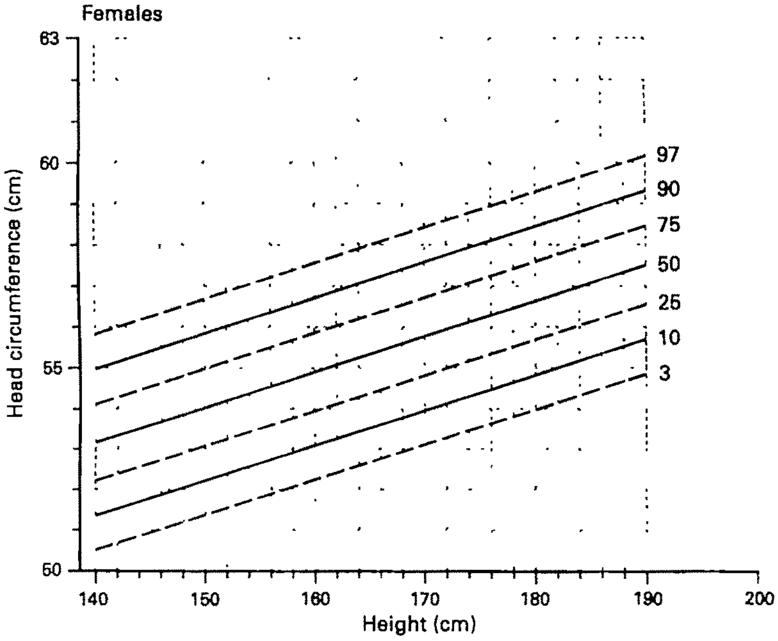

Figure 4 Centile chart for head circumference against height constructed from our data for use in adult females. For comparison, on the Tanner charts the 97th centile for a girl of 16 years is 56·4 cm and the 50th centile 54·2 cm.

Discussion

We have produced centile charts for adult head circumference based on measurements from two British centres (figs 3 and 4). From our measurements it is apparent that it could be quite misleading to make an assessment of an individual's centile for head circumference without taking height into account. This is in agreement with the data of Bale *et al* who showed a correlation between head circumference and height in a small number of normal subjects.[7] A relationship between brain weight and height has also been demonstrated in adult life as well as during childhood.[8]

Most importantly, we have shown that in adult males especially it is quite misleading to use the end of the paediatric charts to plot parental head circumference, as the mean head circumference of a male of average height is above the 97th centile at age 16 on the Tanner charts. This discrepancy is not so marked in females, probably reflecting the fact that the adolescent growth spurt occurs earlier in females than in males and that head circumference in males continues to grow into early adulthood. These charts provide a more accurate reference range to detect abnormal head circumference in adults.

We would like to thank Dr Susan Huson, whose comments on patients with neurofibromatosis type 1 indirectly stimulated this study We would also like to thank Professor Barnes in the department of operative dentistry, University of Newcastle upon Tyne, and Dr Edmunds in the oral health clinic of the dental hospital in Cardiff for allowing access to their patients and staff. The values from the Tanner charts are reproduced by permission of Castlemead publications. KMDB is an MRC Training Fellow. Reprints and copies of the centile charts are available from Dr Bushby

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Immunisation status in inner London primary schools

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Abstract

In one inner London district health authority, the immunisation status of children attending their routine school entry health interview was reviewed over four terms. During the course of these interviews, school nurses completed a questionnaire with parents that asked for their child's immunisation history and details of family and social background. Parental reporting of immunisation history was compared with district health authority records. Only 56% of children reviewed were found to be fully immunised, although a substantial number (386) of the 513 partially immunised children required only a preschool booster. Four percent (54) of the children had received no immunisations; a disproportionately high number of these were recent immigrants. Mechanisms for identifying unimmunised children before they enter communal groups need to be established.

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There has been a dramatic improvement in vaccine coverage among 2 year old children over the past decade in this country. This is partly due to initiatives introduced in district health authorities by immunisation coordinators appointed to manage immunisation programmes.[1] The new target of 95% coverage[2] has been achieved by 62 districts for diphtheria and 40 districts for measles vaccine.[3] There remains a considerable range, however, with lower uptake tending to occur in inner city areas: for example, measles coverage in districts in the South East Thames region ranges between 61 and 95%.[3] For target rates to be achieved and maintained in all districts, additional initiatives may be required. Review of children's immunisation status at entry to communal groups such as nurseries, playgroups, and school has been suggested as a mechanism for identifying children who have fallen through the net, with opportunistic immunisation of children found to be inadequately protected who have no parental objection or medical contraindication.[4]

Access to accurate records is necessary to identify unimmunised children but it is well recognised that discrepancies are common between records held by parents, clinics, general practitioners, and health authorities.[5–7] In inner city areas, with highly mobile populations and many families living in temporary accommodation such as bed and breakfast hotels, maintenance of an accurate child register by the health authority is difficult.[8]

This study was conducted to investigate the feasibility of reviewing children's immunisation status at school entry in an inner London health district, to explore attitudes to the provision of immunisation in schools, and to assess the adequacy of systems used to record immunisation.

Methods

Over a period of four terms from September 1989 to December 1990, in addition to information routinely collected, school nurses in the 33 primary schools in one inner London health authority completed a questionnaire with parents at each child's school entry health interview. Information obtained included details of immunisation status and whether parents had a written record of their child's immunisations. For those children who were not adequately immunised, the reasons were noted and parents asked whether they would like immunisation to be offered in school. Details of family and social background were gathered including ethnic origin, main language spoken at home, family size, parental occupation, and whether the family was living in temporary accommodation.

Information on each child's immunisation status was subsequently validated by comparison with computerised records held by the district health authority of residence.

In addition, each school nurse was sent a questionnaire in confidence to determine their attitudes to the provision of immunisation in primary schools. Information collected included whether immunisation was currently provided in schools, views on school nurses giving immunisations, and the perceived training needs if they were to provide such a service. Head teachers were also sent a questionnaire to explore their current practice regarding assessment of school entrants' immunisation status and their attitudes to schools adopting a greater role in this area.

Results

The number of primary school entrants in the district was difficult to establish and is estimated to be 1555 in one year. School rolls are not held at a central point or on computer by the education authority and the school population is constantly changing because of family mobility. Over a period of four terms information was collected for 1411 children at school health interview; two parents refused to take part. Most children (84%, 1053) were seen by the school nurse within their first year in school. However, 16% (199) had been in school for four

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terms or longer, with 12 terms being the longest interval between school entry and the health interview. Forty three percent (87/199) of children who had been in school for four terms or longer had entered an attached nursery class where health interviews are not conducted.

Nine of the 33 head teachers reported having had more than one case of measles, mumps, whooping cough, or rubella among staff or pupils in school during the last academic year.

AGE AND SOCIAL BACKGROUND OF CHILDREN

Ages of the children at their school health interview ranged from 4·5 to 11 years, although the majority (69%, 981) were aged between 4·5 and 6 years. The majority of children were resident in the district under study (69%, 974) or the three adjoining health districts (27%, 377), with the remainder coming from 17 other health districts in London.

Eleven percent of the children (165), were living in temporary bed and breakfast accommodation, 54% (89) of whom were from the district under study; 21% (300) of children were from single parent families. Their ethnic backgrounds varied widely: the largest group were white and of UK origin (32%, 446), 27% (383) were Asian most of whom originated from Bangladesh (84%, 323), and 12% (167) were black children, 54% (90) of whom were of African origin. Thirty four percent (31) of African and 22% (70) of Bangladeshi children were living in temporary accommodation compared with 5% (22) of white UK origin. For 39% (555) of children, English was not the main language spoke at home. Bengali was the main language for the majority of these families (57%, 314), but 43 other languages were mentioned. An interpreter was available for 205 of the health interviews although in conducting a further 79, the nurses expressed some difficulty with language. Only 1% (18) of children attended the school health interview unaccompanied by a parent or other adult.

Ninety three percent of children (1318) were reported to be registered with a general practitioner; 2% (32) were not registered and for a further 61 children this information was not available. Eleven percent (17/153) of children living in temporary accommodation were not registered with a general practitioner compared with 1% (15/1197) of those living in permanent accommodation.

IMMUNISATION STATUS

Immunisation status was determined on the basis of parental report which for 13% (189) of children could be verified by a record held by the parents. A further 50% (705) of parents said they had a record of immunisation but it was not available at the interview; 17% (241) had no record, and no information was available for 276 children. A health visitor's written summary of preschool health had been received by the school nurses for 38% (532) of the children.

Immunisation status of the children for diphtheria, pertussis, and measles vaccines is shown in table 1. Coverage of diphtheria was similar to that for tetanus and polio and represents uptake of all three antigens. Overall 80% were protected against measles having had measles, mumps, and rubella (MMR) and/or measles vaccine.

Table 1 Immunisation status as reported by parents for 1411 children. Results are % (number of children)

Vaccine	*Immunised*	*Not immunised*	*Not known*
Diphtheria:			
1st	92 (1295)	4 (56)	4 (60)
3rd	89 (1255)	7 (95)	4 (61)
Booster	67 (949)	26 (368)	7 (94)
Pertussis:			
1st	78 (1100)	17 (242)	5 (69)
3rd	76 (1068)	19 (272)	5 (71)
Measles	73 (1033)	20 (286)	7 (92)
MMR	43 (607)	49 (687)	8 (117)

For the purposes of this study full immunisation was defined as a completed primary course of diphtheria, tetanus, pertussis and polio, protection against measles as either measles vaccine and/or MMR, and a booster of diphtheria, tetanus, and polio. Fifty six percent of children (791) were found to be fully immunised as defined above; 36% (513) were partially immunised; and 4% (54) had had no immunisations at all. For the remainder (4%), parents either did not know their child's immunisation status (33) or the information provided was not adequate to determine immunisation status (23).

Of the 527 children who were not fully immunised, the majority (368) lacked their preschool booster with 140 children requiring both a booster and protection against measles. The primary course of diphtheria, tetanus, and polio had not been completed by 94 children and 272 were not fully protected against whooping cough, although 30 of these had commenced the course. One hundred and eighty three children lacked protection against measles, having had neither measles vaccine nor MMR combined vaccine.

Asian children were less likely to be fully immunised than other groups; 50 of the 54 children who had no immunisations were of Asian origin. Fifty two percent (48/92) of children living in homeless families' accommodation were fully immunised compared with 60% (562/932) in permanent housing even after allowing for the Asian group. Forty percent of children who were not registered with a general practitioner were fully immunised compared with 60% of those registered, even after allowing for homeless families.

REASONS FOR INADEQUATE IMMUNISATION

Differing reasons were given for inadequate immunisations against different diseases: for measles, the most common was that the child was a recent immigrant (27%, 49), while 18 parents said they considered the vaccine to be unnecessary because their child had already had the disease. For pertussis, the most common reason given was fear of possible side effects of the vaccine (13%, 36). A number of children had not been immunised against pertussis and measles after advice from health professionals.

Of those children who had had no immunisations, 41 parents gave recent immigration as their reason; a further seven (also immigrant families) said they were unaware of the need for immunisation. Parents of the remaining six, said either that they did not believe in immunisation or were afraid of possible side effects.

Aspects of the service were more likely to be given as the reason for failure to obtain a child's booster injection: an appointment for immunisation had not been received by 17% (62) of parents. Forty children were delayed in completing their primary course and for 25% (92) the parents said they had not got round to taking their child for the booster.

Parents of children who were not fully immunised were asked whether they would like their child to be immunised at school; 69% (317/457) were in favour of this, but 89 of the remainder (126) said they would prefer to go to their general practitioner or clinic.

VALIDATION OF IMMUNISATION STATUS WITH DISTRICT RECORDS

The immunisation history of each child was checked with records held by their district of residence. No records were available for 40% (571) of children in the study; this includes older children who may not have been entered onto a computerised system but 30% of records were not available for children younger than 6 years. Immunisation status could not be validated for a further 19 children as no identifying information had been collected at interview. Records were not available for 50% of children living in temporary accommodation compared with 39% of those who were not and for 48% of Asian children compared with 38% of children of white UK origin.

Immunisation rates of 821 children for whom a record was available were compared with parental reports and are shown in table 2. Apart from the reporting of MMR vaccine, parents consistently reported higher immunisation rates than districts.

Examination of district records also showed that by three months after their school health interview, 90 children had received further immunisations; the majority of these were MMR and/or boosters.

SCHOOL NURSES' ATTITUDES TO IMMUNISATION

Eighty percent (12/15) of school nurses responded to the questionnaire. Although eight of the nurses had experience of immunising children, all were generally opposed to immunisation in school; three thought it could be appropriate as a last resort. Reasons given were that it is not good practice and that it is unnecessary because adequate provision already exists. Seven nurses considered that school is not the most appropriate place for immunisation and that it would create problems such as children becoming upset and difficult to settle in class, and would associate school with injections; that it would take up too much time and that there was a lack of adequate facilitites such as for the disposal of waste. Five nurses mentioned that teachers would not wish immunisation to take place in school.

The nurses were not in favour of giving immunisation themselves as they did not perceive it as fulfilling a health education role; six felt it would be detrimental to their relationship with the child. Only three nurses felt adequately trained to give immunisation, and even then would want a doctor on the premises, while seven said they would require a complete practical and theoretical update and four training on the management of anaphylaxis. Even with appropriate training, eight nurses would not be willing to give immunisation under any circumstances.

Table 2 Comparison of parents' reports of immunisation rates with district records for 821 children. Results are % immunised

Vaccine	*District health authority record*	*Parent record/recall*
Diphtheria:		
1st	83	97
3rd	76	96
Booster	68	73
Pertussis:		
1st	71	85
3rd	66	83
Measles	70	80
MMR	53	51

HEAD TEACHERS' ATTITUDES TO IMMUNISATION

Ninety four percent (31/33) of the head teachers responded to the questionnaire. Only two were currently asking parents for details of their child's immunisation status before they entered school and both advised parents of the need for immunisation and how to obtain it if necessary. Of the remaining 29, 20 said they would be prepared to include a question about immunisation in their routine admissions procedure, and 19 to recommend that parents should have their children fully immunised before school entry. Fifteen of the head teachers thought that immunisation should be offered at the school health interview for inadequately protected children, and 16 thought a special immunisation clinic should be provided in school. Head teachers who opposed immunisation in school gave similar reasons to those given by the school nurses: that immunisation is the parents' responsibility, a health and not an educational matter, would cause disruption to classes, and would affect the child's relationship with the school nurse.

Discussion

The school as a setting is well suited to the production and spread of epidemics.[9] Children who are not fully immunised on entering school are particularly likely to transmit disease within the school community and also to place younger siblings at risk. Parental reports are likely to be an over estimate of immunisation status,[10] and particularly inaccurate for older children,[11] but this study demonstrates that based on parents' reports, a proportion of children entering primary schools in an inner London district are inadequately immunised. Based on district figures the proportion not fully protected is even larger. This includes vulnerable children living in homeless families' accommodation where transmission of infection is particularly likely, and children whose families have recently immigrated, often from countries where diseases such as polio and diphtheria are still prevalent. It is of particular concern that 4% (54) of children had had no immunisations at all; the majority of these parents did not object to immunisation but were unaware of its advisability.

The policy in the district under study is to offer a health interview within the first year of primary school entry and although this was carried out in the majority of cases, a proportion of children were in school for a considerable period before they were seen and their immunisation status assessed, increasing the likelihood of exposure to infection. Susceptible children need to be identified and immunised before entry to nursery class or primary school in order to prevent outbreaks of disease. This can only be achieved with the cooperation of head teachers and the education authorities. Our findings suggest that many head teachers would be prepared to inquire about immunisation status in their admissions procedure. Such a scheme has proved successful in Tower Hamlets where a growing number of schools include a question about immunisation.[12]

The ability of school nurses to give vaccines on the school premises along with recording of immunisation status has been shown to be critical to the success of programmes aimed at increasing immunisation rates in the school population.[13] In this study school nurses were found to be reluctant to administer immunisation, but the training of nurses is increasingly encouraged and has been shown to be an important approach in ensuring that hard to reach children are given protection.[14] If the majority of susceptible children were identified and protected before school entry, school nurses would have to immunise only a small number: those who may have had no previous opportunity and/or reduced access to primary health care services.

Recording of immunisation is still largely inadequate and this study highlights the particular difficulties in inner London. Many districts are now introducing parent held health records as the child's main health record. These have proved to be popular with both parents and health professionals, to be completed accurately, and to be readily available at each health service contact.[15] National use of these records with standardisation of the immunisation component would facilitate identification of unimmunised children and encourage opportunistic immunisation. It is important that all health professionals involved in immunisation are aware that completing a record of vaccines given is an essential part of the immunisation procedure. Reliability and completeness of records and accurate evaluation of vaccine coverage would be improved if standard procedures were established for relaying data to the core information system within districts. Increasing population mobility also necessitates compatibility of systems for transfer of data between districts.[5]

The aim is to ensure that children are protected from infectious disease as early as possible and the recently introduced accelerated immunisation schedule has been a contributory factor in improving vaccine coverage among young children.[1] However, if childhood infectious diseases are to be eliminated, mechanisms for identifying unprotected children, such as review of immunisation status at school entry, must be established.

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Archives of Disease in Childhood 1992; 67: 1292–1293

An audit of preschool vision screening

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Abstract

An audit was carried out to clarify the dispute surrounding the vision screening test at 3·5 years. The uptake was 53·5%, sensitivity 77%, specificity 96%, and positive predictive value 50%. In particular the uptake was poor and the test needed a clear policy for the future.

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The vision screening test at 3·5 years of age aims to find 'cases' of reduced visual acuity, amblyopia, and squint. Opinion is divided about its value,[1–5] and a recent report on child health surveillance recommended that it should be discontinued.[3] This debate together with the emerging role of the community orthopist prompted an audit to find out 'what was happening' and 'what should be done'. The performance of the test was evaluated by measuring its uptake, sensitivity, specificity, and positive predictive value.[6]

Subjects and methods

The target population was 1365 primary schoolchildren in Lancaster born between 1981 and 1983. A random sample of 599 school health records provided the data. Special schools were not included.

The test of visual acuity in school entrants was used as the reference test and was recorded in 531 children, which formed the eligible population for this study. A positive case was defined as a visual acuity of 6/12 or worse in either eye and squint was excluded. The 531 records were inspected and the validity of the screening test result classified according to the outcome of the reference test.[6] Records of false positives were checked to take account of the possible effects of any treatment on classification.

The vision screening at 3·5 years was carried out by clinical medical officers using the Stycar vision test with five single letter matching at 3 metres (mean age 3·5 years). The reference test was carried out by school nurses using the Stycar vision test with seven single letter matching at 6 metres (mean age 5·1 years).

Results

At 5 years the prevalence of reduced visual acuity in either eye was 6/12 or worse in 4·5% (24/531) and 6/18 or worse in 2·1% (11/531).

Table 1 Uptake of the vision screening test at 3·5 years (n=531) Results are number (%)

Missing preschool records	*No recording*	*Did not attend*	*Did not cooperate*	*Uptake*	*Total*
39 (7 3)	93 (17·5)	63 (11 9)	52 (9 8)	284 (53 5)	531 (100)

Table 2 A comparison of the reference test to the outcome of the screening test (n=284)

	Reference test		
	Positive	*Negative*	*Total*
Screening test:			
Positive	10	10	20
Negative	3	261	264
Total	13	271	284

Table 1 shows the uptake of the screening test. In the 63·3% (336/531) who attended, 84·5% (284/336) cooperated. The largest single group (17·5%) with no test at 3·5 years had no evident recording in the notes and 49% in this group were children who had transferred into Lancaster.

Table 2 shows the results of comparing the reference test to the outcome of the screening test. The sensitivity was 77% (10/13), specificity 96% (261/271), and positive predictive value 50% (10/20).

In the 10 false positive cases (table 2) that were followed up for the possible effects of treatment, nine received no treatment and one was lost to follow up.

Discussion

An audit should compare results with standards but in their absence comparisons were largely confined to peers: orthoptists,[1 2 4] health visitors,[2] trained nurses,[5] and a paediatrician.[5] All these authors included squint in their studies.

The attendance of 63% was poor when compared with 95%[5] and 70–75%[4] but was akin to 67%[1] and a coverage of 60% (orthoptists) and 59–84% (health visitors).[2] The cooperation of 84·5% was also poor and other authors report 95%[4] and 98%.[5]. The final uptake of 53·5% in this study was low compared with a reported 93%[5] and 63%.[4]

Some explanation should be offered for the poor results shown in table 1. The absence of records and poor record keeping of the vision test at 3·5 years highlights some of the administrative difficulties in record keeping in the community. There was a large group with no recording of the test at this age, however 49% of this group had transferred into the district. There is, however, little excuse for the lax recording in the remaining 51%. It is unlikely that incorrect addresses were a significant cause of failure to attend as these were checked before the appointment. Neither can failure to attend be attributed wholly to poor socioeconomic factors as Lancaster is a rural district with a good vaccination uptake. It is likely that the assessment was unpopular or unacceptable to clients.

In the screened population the sensitivity of 77% compares with results achieved by others: 90%[1] and 100% (orthoptists) and 43% (health visitors).[2] The high specificity of 96% was similar to 99%[1] and 98–100%.[2] A positive predictive value of 50% indicates excessive over referrals and compares poorly with others who have obtained 94%[1] and 74% (orthoptists) and 100% (health visitors).[2] False positives are a hazard of screening causing unnecessary work for staff and concern to clients.

The study can be criticised for the length of time between the screening and the reference test. Amblyopia might have developed and an improvement might have occurred under possible treatment in the one case that could not be followed up. We do not, however, consider that the values of performance would have been significantly affected. Furthermore a more extensive study would have included squint and an ophthalmological opinion. Nevertheless the work was revealing enough when confined to visual acuity. When considering 'what should be done' any decision should be based on the standard prerequisites for screening.[7]

The test was largely unacceptable with a poor sensitivity and positive predictive value. There was no evidence of a controlled study showing effective treatment for amblyopia. Clearly the prerequisites for a screening programme were not met and the test in Lancaster was manifestly unsatisfactory. However, it is easier to refrain from embarking on a programme than to dismantle an existing one that has public expectations.

The developmental assessment at 3·5 years together with the vision screening test has been transferred to health visitors and high standards of ongoing training are a clear necessity. A poor uptake was a significant problem and as health visitors work on a domicillary basis an increased uptake can be expected.

The cycle of audit in this study requires completion and there is a need for a controlled trial demonstrating the effective treatment of amblyopia. The wealth of paperwork in the community health services is fertile ground for further work in audit.

We are indebted to Joanne Huntington for her patience and skill with the typing and Manet for her support.

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Microfollicular thyroid adenoma and congenital goitrous hypothyroidism

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Abstract

Three patients with congenital goitrous hypothyroidism are reported. They were treated with adequate thyroxine replacement and developed well defined microfollicular thyroid adenomas despite being euthyroid clinically and biochemically throughout their clinical course. Patients with congenital goitrous hypothyroidism appear to be at increased risk of developing thyroid adenoma in childhood despite the use of replacement thyroxine treatment in physiological doses.

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Congenital goitrous hypothyroidism due to a primary biochemical defect of thyroid biosynthesis accounts for approximately 10–15% of all congenital hypothyroidism detected at screening in Western countries.[1] The goitre is presumed to be due to thyrotrophin stimulating hormone (TSH) overstimulation in response to low thyroid hormone concentrations causing hyperplasia of the dysfunctional thyroid tissue.[2] This process may lead to the development of adenomatous growth and rarely malignant transformation.[2] We report three patients with this condition who developed well defined, encapsulated microfollicular adenomas despite adequate thyroxine replacement.

Case reports

CASE 1

A boy was referred at the age of 3·3 years with a goitre present since birth. Clinically he was euthyroid. Investigations revealed free thyroxine index (FTI) 95 (normal 65–150), TSH 32 mU/l (normal <7), and a diffusely enlarged goitre with avid uptake on a technetium thyroid scan. The perchlorate discharge test did not suggest a peroxidase deficiency.

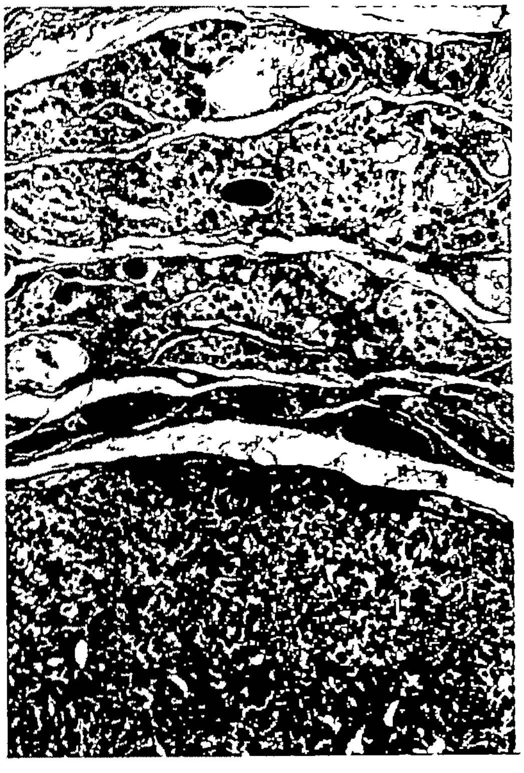
When thyroxine treatment was given the gland regressed to a normal size. Thyroxine requirements were monitored by thyroid function studies and TSH measurements at intervals of three to six months. He remained euthyroid clinically and biochemically and at the age of 11·7 years presented with a thyroid nodule. Ultrasonography revealed mildly enlarged thyroid lobes, and a well defined solid mass in the left lobe. At operation a 1·8 cm diameter microfollicular adenoma of fetal type was removed.

CASE 2

This girl was detected on the neonatal screening programme at the age of 2 weeks and a diagnosis of congenital goitrous hypothyroidism secondary to peroxidase deficiency was made on the basis of avid uptake on thyroid scan and a positive perchlorate discharge test. The initial thyroid function tests were triiodothyronine resin uptake 0·65 nmol/l (normal 0·80–1·20), thyroxine 18 nmol/l (normal 100–215), FTI 12 (normal 75–200) and TSH 620 mU/l (normal 1–15).

Her thyroxine replacement was monitored at intervals of three months, and throughout the next four years the TSH remained <7 mU/l except for two occasions (at the age of 2 and 4 years) when it was transiently increased, reaching concentrations of 17·5 and 11·5 mU/l respectively. The FTI remained in the range 126–192 at all times (normal 50–180).

At the age of 4·25 years a thyroid nodule was detected clinically. A thyroid scan revealed a hyperfunctioning thyroid nodule in the left lobe. At operation a 2 cm diameter microfollicular adenoma of fetal type was removed. A similar 0·2 cm adenoma was present in the adjacent thyroid tissue. The follicular epithelial cells showed variable hyperplasia and nuclear enlargement (figure).



Adenoma and adjacent hyperplastic thyroid tissue of case 2 (haematoxylin and eosin ×130).

CASE 3

This boy had congenital goitrous hypothyroidism diagnosed at 9 months of age when he presented with the classical clinical features of hypothyroidism. This was confirmed by the thyroxine measurement of 30 nmol/l (normal 75–160) and TSH >400 mU/l (normal <7). The thyroid scan showed an enlarged thyroid gland with moderately enhanced but uniform uptake.

Replacement thyroxine treatment was started with a good clinical and biochemical response. His thyroxine and TSH remained within normal ranges throughout the next 11 years.

At the age of 12·5 years he presented with a nine month history of a nodular goitre. On palpation the left lobe was 5×4 cm and the right 3·5×4 cm. Thyroid ultrasound identified multiple solid nodules involving both lobes of the thyroid gland. The largest mass measured 3×3×3·5 cm in the left lobe and corresponded to a large well demarcated solid nodule.

Total thyroidectomy was performed. The cut surface showed several well demarcated colloid nodules with a 2·5 cm diameter fleshy nodule in the left lower lobe. The large nodule in the left lobe was well circumscribed follicular adenoma showing microfollicular and embryonal growth pattern. Elsewhere in the thyroid tissue there were numerous nodules showing quite variable cellularity.

Discussion

These patients had hypothyroidism secondary to dyshormonogenesis. The positive perchlorate discharge test in case 2 suggests an organification defect,[3] while the normal perchlorate discharge test in case 1 would suggest a diagnosis of one of the other metabolic abnormalities such as deiodinase, coupling, or thyroglobulin defects.[3] All remained euthyroid clinically and biochemically but despite the seemingly adequate thyroxine replacement they developed microfollicular adenomas.

Histologically, congenital goitrous hypothyroidism is characterised initially by diffuse hyperplasia. Nodules and adenomas develop over time and typically are very cellular, showing embryonal or fetal architecture.[2] As a result the histological distinction between adenoma and nodule may not be clear cut. Hyperplasia and cellular pleomorphism may be so marked as to mimic malignant transformation, but genuine malignancy appears to be a rare event, only six cases being accepted in the literature review of Cooper *et al.*[2]

In contrast to our patients, most cases previously described were long term hypothyroid or on sporadic thyroxine replacement with excessive stimulation of TSH. Our patients unexpectedly developed true adenomas despite strict clinical and biochemical follow up, suggesting sensitivity of the patients' thyroid follicles to the effects of normal TSH concentrations. This is supported by the histological observation of diffuse hyperplasia in cases 2 and 3 as well as the presence of multiple small adenomas in case 3. Recent evidence suggests that there are many other thyroid growth promoting agents including vasoactive inhibitory peptide[4] and epidermal growth factor.[5]

We conclude that although patients with congenital goitrous hypothyroidism are partially protected from the development of nodular goitre by adequate thyroxine replacement treatment, they remain at risk of developing follicular adenomas as a result of persistent low concentration TSH stimulation. Thyroxine replacement treatment will reduce but not eliminate the development of adenomas.

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Archives of Disease in Childhood 1992; 67: 1296–1297

Oral hairy leukoplakia in vertically and horizontally acquired HIV infection

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Abstract

Two boys aged 7 and 8 years, respectively, with oral hairy leukoplakia as the sole clinical sign indicative for HIV infection are reported.

(*Arch Dis Child* 1992;67:1296–7)

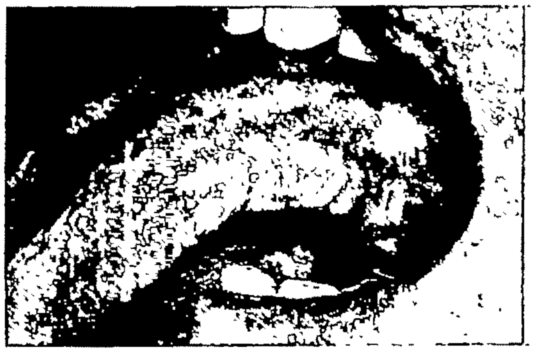
Oral hairy leukoplakia, a mucosal lesion termed so because of its 'hairy' appearance, is commonly observed in adults with advanced HIV infection.[1] We report on two boys aged 7 and 8 years, respectively, in whom physical examination revealed oral hairy leukoplakia as the sole clinical sign indicative for HIV infection.

Case reports

CASE 1

This boy was first seen in our outpatient clinic at the age of 7 years. He was referred because his mother had recently had encephalopathy due to AIDS diagnosed. The father was an intravenous drug abuser who died of an overdose shortly after the boy's birth. After an uneventful pregnancy, the boy was vaginally delivered at term. The neonatal period was uneventful. No information could be gathered about breast feeding. During infancy, the boy experienced recurrent upper respiratory tract infections that did not require antibiotic treatment or hospitalisation. At the age of 2 years the child moved with his mother to Ecuador. He returned to Switzerland only one month before referral. Except for several episodes of diarrhoea associated with amoebiasis his history was uneventful.

On physical examination the boy had height, weight, and head circumference on the third centile for age. Lymph nodes, liver, and spleen were not enlarged. Neurological and neuropsychological tests were normal. However, whitish, vertically oriented bandform lesions, each 0·3–0·5 mm in width, were noted on the posterolateral margins of the tongue (figure). The lesions could not be scraped off and a Gram stain of a swab showed no yeast. Epstein-Barr virus DNA was detected by Southern blot analysis of DNA extracted from cells scrubbed from the lesions and amplified using the polymerase chain reaction and two oligonucleotide primers from the Bam H1 W fragment of the virus. Chest radiographs showed no lymphoid interstitial pneumonitis. Infection with HIV was established by serology, detection of circulating p24 antigen, and positive viral blood cultures as well as polymerase chain reaction for HIV genome. The CD4+ cell count was 40×10^6/l; lymphocyte proliferation to recall antigens was absent and poor to stimulation with mitogens.



Clinical appearance of oral hairy leukoplakia Note the characteristic vertical mucosal folds with the whitish lesions

CASE 2

This boy was referred at the age of 8 years. Because of recurrent episodes of fever, recurrent bronchitis, and increasing fatigue in the previous six months, his paediatrician had asked for the presence of antibodies to HIV to be tested as well as routine laboratory investigations; antibodies to HIV were present. The parents were seronegative for HIV. The boy's history revealed that he had been transfused packed erythrocytes at the age of 5 weeks when he was treated at another hospital because of sepsis. Then, serological tests for antibodies to HIV were not yet available. The blood donor, who since then had abstained from further donations, was traced and found to be infected with HIV. At the age of 4 years the boy had manifested haemolytic anaemia and thrombocytopenia that resolved after transfusion of intravenous gammaglobulin. HIV as possible cause had not been sought at that time.

On referral, the boy showed normal growth, slightly enlarged lymph nodes, and no hepatosplenomegaly. On both lateral margins of the tongue whitish lesions were noted. These lesions were similar to the ones reported in case 1. Also, as in case 1, Epstein-Barr virus DNA was detected in scrape material from the lesions. Peripheral blood was positive for HIV genome by polymerase chain reaction and grew HIV in culture. No lymphoid interstitial pneumonitis was seen on chest radiography. The CD4+ cell count was 50×10^6/l; there was no proliferation of the lymphocytes to stimulation with recall antigens or mitogens.

Discussion

In adults oral hairy leukoplakia is, in the

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absence of long lasting iatrogenic immunosuppression,[2] pathognomonic for HIV infection.[1] Association with progression to AIDS within few months is common. Epstein-Barr virus has been implicated as cause of the lesion.[1] Distinction from thrush, which can be removed mechanically and be recognised by Gram stain, is easy. Differential diagnosis includes the rare white sponge naevus, frictional keratosis, some forms of lichen planus, and idiopathic leukoplakia. There is no established treatment for the lesion itself.[3]

We have found only one child reported in the literature, aged 8·3 years, who had oral hairy leukoplakia.[4] So far, the disorder seems to be rare in children infected with HIV. But this may be due to the relatively long interval between acquisition of HIV and manifestation of the mucosal lesion. Horizontal transmission of HIV via blood products as in case 2 should be prevented now that the routine testing of donors for antibodies to HIV has been introduced. However, with the AIDS epidemic ongoing, a growing number of children vertically infected with HIV can be anticipated. As a large proportion survives longer than six years,[5] many of these children will reach school age and may be oligosymptomatic or even asymptomatic, as in our case 1. Infection with HIV may therefore go unrecognised, especially when the parents are not aware of a risk for HIV infection or when they do not report such a risk while they are relatively well. Thus, in asymptomatic children seen by a general practitioner, for example for routine immunisation, oral hairy leukoplakia may be the sole sign indicative for HIV infection. Hence, simple careful clinical examination may lead to diagnosis and have an important impact, because advanced immunodeficiency may demand antimicrobial prophylaxis against opportunistic agents or initiation of antiretroviral treatment.

1 Greenspan JS, Greenspan D, Lennette ET, *et al.* Replication of Epstein-Barr virus within the epithelial cells of oral 'hairy' leukoplakia, an AIDS-associated lesion *N Engl J Med* 1985,313:1564–71.
2 Schmidt-Westhausen A, Gelderblom HR, Hetzer R, Reichart PA. Demonstration of Epstein-Barr virus in scrape material of lateral border of tongue in heart transplant-patients by negative staining electron microscropy. *J Oral Pathol Med* 1991;20:215–7
3 Katz MH, Greenspan D, Heinic GS, *et al*. Resolution of hairy leukoplakia: an observational trial of zidovudine versus no treatment. *J Infect Dis* 1991;**164**:1240–1.
4 Greenspan JS, Mastrucci MT, Leggott PJ, *et al.* Hairy leukoplakia in a child *AIDS* 1988;2:143
5 Tovo PA, de Martino M, Gabiano C, *et al*. Prognostic factors and survival in children with perinatal HIV-1 infection *Lancet* 1992,339:1249–53.

Archives of Disease in Childhood 1992; 67: 1298–1301

CURRENT TOPIC

Building a combined child health service

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The fragmentation of health services for children has been recognised as unsatisfactory for at least 15 years.[1] Children cannot themselves complain about this and those of us working for them have been slow to tackle the problems that had to be surmounted in order to achieve integration. This paper outlines the need for this integration and suggests how to achieve it, based on the experience of West Dorset.

Why integrate?

It is logical. The existing fragmentation into at least two and often three units or trusts in any district creates boundaries that are not designed to be cohesive and inevitably create gaps and overlaps in any service which has to cross them. Figure 1 is the management structure in West Dorset before and, figure 2, after integration. This illustrates the complexity of child health services whatever system of management operates, and the simplification which integration allowed.

Children require a whole service

The gaps, overlaps, and fragmentation can never provide a whole service for the whole child. Every district has its own examples of working together with the best of intentions but often in opposite directions. Examples of such situations are given and referred to under subsequent headings. All of them apply under this particular heading.

Other carers and agencies require it

There are frequent complaints of 'buck passing'

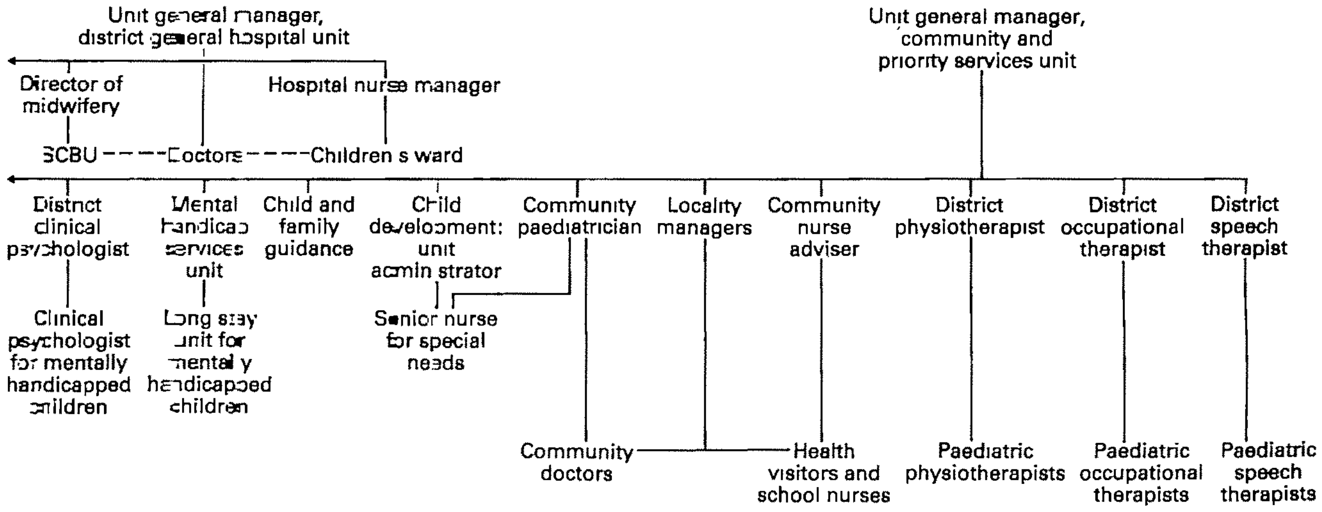
Unit general manager, district general hospital unit
Director of midwifery
Hospital nurse manager
SCBU
Doctors
Children s ward
Unit general manager, community and priority services unit
District clinical psychologist
Mental handicap services unit
Child and family guidance
Child development unit administrator
Community paediatrician
Locality managers
Community nurse adviser
District physiotherapist
District occupational therapist
District speech therapist
Clinical psychologist for mentally handicapped children
Long stay unit for mentally handicapped children
Senior nurse for special needs
Community doctors
Health visitors and school nurses
Paediatric physiotherapists
Paediatric occupational therapists
Paediatric speech therapists

Figure 1 Management of children's services before integration; SCBU=special care baby unit.

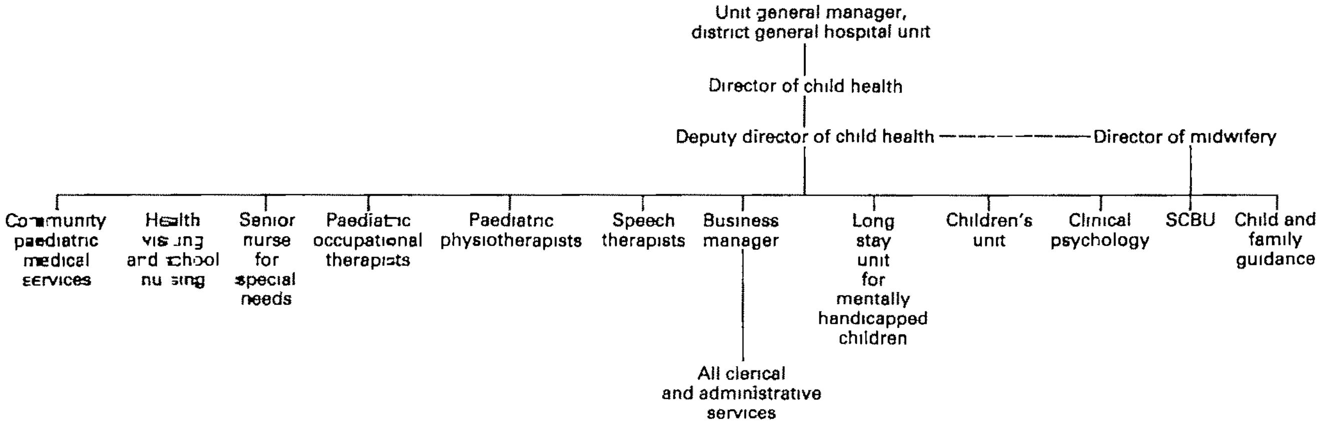
Unit general manager, district general hospital unit
Director of child health
Deputy director of child health
Director of midwifery
Community paediatric medical services
Health visiting and school nursing
Senior nurse for special needs
Paediatric occupational therapists
Paediatric physiotherapists
Speech therapists
Business manager
Long stay unit for mentally handicapped children
Children's unit
Clinical psychology
SCBU
Child and family guidance
All clerical and administrative services

Figure 2 Management of children's services after integration, SCBU=special care baby unit.

and inaccessibility of the service from general practice, social services and education, and parents are completely bewildered by the divisions and splits which prevent their children receiving an effective service (see example 3 particularly).

Policy making requires it

The majority of policies or good practice guidelines that relate to the health of children involve contributions to the overall service from several units or agencies (see example 4).

Policies and protocols are only effective if they are then 'owned' by all the members of the groups involved, from management level to field workers and clerks. This can happen if there is clear accountability for creating a policy and then putting it into operation.

Purchaser/provider split requires it

The division from the old health authority units into a purchasing health authority and provider trusts or directly managed units threatens to increase the feeling of fragmentation for workers within the service. Priorities for contracts and funding may be quite different from one trust to another (see example 5).

Recruitment requires it

There are certain professional groups, such as speech therapists, clinical psychologists and, in some areas, health visitors, which are in short supply. Applicants can choose from the many districts with vacancies, who then find themselves competing to attract new staff. A well organised integrated department that has clear standards and policies is far more attractive to these applicants and quite soon generates a confidence which gives the district a good reputation. It is not long then before advertisements start to produce a choice of field, which in turn enhances the quality of the department as a whole. West Dorset found this particularly true in the speech therapy department, and the prolonged vacancies that used to be a frequent feature now seem to be a thing of the past.

Examples

EXAMPLE 1

A young child with profound disability discharged from hospital, with the assurance to his parents that there will be prompt visits from their health visitor and respite care arrangements made. These arrangements were mentioned in the discharge summary from ward sister to health visitor and ward doctors to general practitioner (GP) but nobody actually referred the child to the respite panel, nor checked that there was a health visitor in post at the time Under the integrated system the ward sister telephones the senior health visitor or liaison health visitor directly and requests both a visit to the family and a referral to the respite care panel. This does not depend on the ward sister's good memory, as it is part of a written policy and the procedure is known to the consultant paediatrician, ward sister, senior health visitor, etc.

EXAMPLE 2

A child with enuresis referred to the outpatient department by his GP The acute paediatrician recommends an enuresis alarm and suitable follow up, writes to whichever agency he believes supplies this service but finds when he sees the child three months later that the alarm has never been supplied. This is because the alarms are held under the incontinence budget of the community unit which is overspent and every request has to be assessed and vetted by the continence adviser who has a very long waiting list. Under the new system an overall policy for the management of enuresis is agreed, the consultant paediatrician knows that he refers direct to the school nurse for that child's school, who keeps her own stock of alarms and, if she has a waiting list, can alert her senior nurse who must monitor that the general waiting list standards for the whole department are met—that is, assessment must be within six weeks of referral and treatment initiated within 12 weeks. In neither situation does the child actually get the alarm any sooner but in the second, everybody knows exactly what is happening and the family do not feel ignored.

EXMAPLE 3

A child with cerebral palsy requiring specialised seating in order to be in a position where he can carry out school work. The health service has supplied seating at home for mealtimes; the education department considers that it has no budget for such specialised seating in school and social services will not contribute to meet the child's needs within school. The education department's links are with the consultant paediatrician who is unaware of the complexity of this problem so writes angrily to the district physiotherapist in the community unit who has no links with the other agencies. Under the integrated service the department of child health's management group can tackle the whole problem by delegating one person, for example, the community paediatrician, to get the relevant agency staff together. Recommendations from these staff should lead to an effective, united interagency bid, for example, to joint finance, to cover any specialised seating requirements within schools. Such bids carry weight because they have a clear policy and recommendations behind them and the united voice of relevant departments and agencies expressing them.

EXAMPLE 4

Creating a policy for management of the dying child requires first of all a decision that this is necessary and then delegation of a convenor to draw up a working party and make recommendations. Under a fragmented system the working party recommendations may only be taken up in part by one unit so that the management of such a child within hospital may become excellent but with none of the recommendations met when he goes back home, or vice versa. Under an integrated system the recommendations can be discussed and converted into policy which is then effective because it is clearly owned by the whole department. It also makes it possible to promote and publicise the policy among the wide range of professionals involved in this sort of situation.

EXAMPLE 5

A child with severe learning disability who has reached adulthood must transfer from all the services who have supported him and his family throughout childhood to, not only new services and service givers, but a whole new trust or unit. Under the fragmented system this could work in some cases where the child was well known to a community team who dealt with children and adults but may not work at all where a child has been predominantly hospitalised or away at residential school and therefore not known to the community team. In an integrated department the two trusts or units can already have been asked to draw up a contract which includes effective overlap of services so that hand-over is planned during the last two or three years of childhood, wherever the child is, so that the adult services have a clear picture of that particular young person's needs before they take on full responsibility for meeting them

Who and what to include?

It is essential to start off with the inclusion of obvious main groups of child health services: the paediatric ward(s), special care baby unit, paediatric intensive care, community paediatrics, school health, and paediatric therapists. There are other important departments that must be included at an early stage, no matter what the difficulties in doing so: child and family guidance, health visiting, mental handicap services, and clinical psychology.

In West Dorset the groups that required more discussion and compromise than others were the special care baby unit, health visiting, clinical psychology, and speech therapy. *The special care baby unit* had been run as part of the maternity unit and its nurse management line was not the same as that for nurses in the children's ward. It was agreed that the nurse manager for midwifery would relate to the director of child health over all matters in the special care baby unit but the budget stayed with the acute unit manager and was not separated out to child health. Once it was found that the new department worked, it became uncontentious to hand over the budget for the unit and this experience eased the way for the eventual inclusion of midwifery/obstetrics into the same department when, two years later, it became the department of maternal and child health.

Health visitors were invited to meet the director of child health very soon after his appointment. He put forward his management philosophy (see later) and asked if health visitors agreed that these ideas were fundamental to them and if so, he invited them to join him in the department of child health. There were of course many anxieties expressed and felt over the early weeks and months, particularly relating to the generic work of health visitors but they joined the department by consent, not coercion.

A similar agreement was made with *speech therapists,* again making clear, in all documents as well as verbally, their continuing generic role.

Clinical psychology was embryonic, being only a recognition by the district clinical psychologist that some behaviour modification advice was necessary for children with learning disabilities! It has since been possible to appoint a full time clinical psychologist within the department of child health and this is an area for further development in the near future.

It is logical to include *obstetrics, genetics, and all antenatal services* within the integrated department. Each of these may be quite a big step to take and may be achieved more easily once the department of child health is seen to be up and running with an identifiable management. In West Dorset the maternity and gynaecology services were integrated after the department had been running for two years and a system of clinical directorates was introduced for all specialties.

Paediatric surgery—general, ear, nose, and throat (ENT), eyes, other specialties—should also eventually be included but will certainly take time to achieve. The most important step initially is to assist surgeons to see children as a separate group and not as 'mini' adults and a group whose needs are already well defined in the recent guidelines published by the National Association for the Welfare of Children in Hospital.[2]

Tertiary services—paediatric cardiology, oncology, neurology, and urology, etc, should be formally linked to the department of child health even though they will usually be in another unit or trust or district altogether. Informal discussions that eventually lead to formal contracts between each of these specialties and the department of child health is one way of achieving this.

All administrative staff relating to all the included departments, should be brought within the department of child health under an overall business manager. This requires some negotiation where staff have divided posts, for example in community clinics where they may cover a range of jobs. By including them from the beginning their loyalty to child health itself can grow because they feel part of a whole service.

Where will the main problems lie?

ORGANISATIONAL BOUNDARIES

Initially these will be in the breaking down of previous fixed structures or professional allegiances—for example, children's wards in acute services, school health and health visiting in community services, the special care baby unit in midwifery services, ENT patients in ENT wards, etc. Professional bodies such as the Health Visitors' Association and other therapists' associations may intervene and require individual discussion and reassurance in order to gain their support for the changed management of their members.

WORK WITH OTHER AGE GROUPS

There may be concern that generic services such as health visiting and speech therapy will be prevented from continuing their work with age groups other than children. Again, discussion and reassurance are required and written recognition of their responsibilities to other age groups should be made in every document.

INDIVIDUAL AND COLLECTIVE ANXIETIES

Supporting people during change is a management skill that is particularly required in the NHS. All must have an opportunity to ask questions and air concerns and positive, truthful answers are essential. Repetition of the department's philosophies, coupled with assurances that professional advisory links will be maintained, can reassure most staff. There are a few whose fears will cause them to rage and rebel against the new structure and they too must be heard and answered but they have an agenda of their own and cannot be allowed to prevent the whole movement from going forward.

MANAGERS

The director must be appointed at a very early stage once a policy of integration has been agreed. It should be a clinician if clinical directorates generally are the district's intention and in most places it is likely to be one of the paediatric consultants; (s)he has to learn fast how to be a manager. The department's model must not be a medical one, nor yet a nursing one, but a new model for children and its philosophy must, in reality not just in lip service, be to meet children's needs and not necessarily those of the staff.

Obtaining a service manager of a high enough grade and experience to make the early stages of the integrated department work smoothly is essential in order to achieve the inevitable changes and make them tolerable for all concerned. A policy of 'slotting in' existing senior staff is unlikely to answer children's needs. There is a real danger of writing a job description to fit the person, rather than the post and this can only be resisted if it is clear from the beginning that the post will go to open advertisement. Some senior staff may well be encouraged to apply but others—those who are negative, those who need their halo to shine, those who are nice but with little management experience—should be told honestly from the beginning that they are unlikely to be suitable for the post.

An administrative or business manager is also needed in order to integrate the running of such a widespread department—from the hotel services of a children's ward to the administrative jigsaw of the school health service. Again, this post is most likely to be satisfactorily filled if it is advertised on an open market.

DEFINITION OF A BUDGET

Drawing up a realistic budget from the dispersed structure of children's services that spans several units or trusts requires cooperation from each of the relevant finance departments and the perseverance of the department's service manager. There may be much negotiation involved to get the budgets set high enough for at least the possibility of being within budget at the end of the first financial year.

DEPARTMENTAL HEADQUARTERS

The siting of the new integrated department in one or other unit or trust is a fairly arbitrary placement, though it is likely to cause much discussion and concern among those who actually have to move from one unit to another. When West Dorset planned its integration the idea of contracting for services between units was a new one but that is now common practice so poses no problem. In fact West Dorset started off in the community and priority services unit but when trust status was introduced, moved into the general hospital trust.

How to start

There must be a 'critical mass' of senior staff willing to integrate in order to take the initial steps. It is not necessary for all of these to be from one discipline but it is likely to be difficult to achieve if there is not a majority of consultant paediatricians who are in agreement. The initial discussions must lead to a strategy document addressing issues such as those outlined above and showing how integration will proceed.

The department's philosophy must be defined and stated at the start of the strategy document. To be convincing and create an effective service, these philosophies must be along the following lines:

- To meet the health service needs of all children living in the district;
- To meet these needs within the context of the family;
- To view childhood as a time of growth and development and not as 'mini' adulthood;
- To view prevention as a principal theme of the services offered.

The framework for the department, and its siting within the district's management system, must be worked out with unit/trust managers. At the same time the job description and salary grading for the new post of service manager must be agreed so that there is as little delay as possible before this important post is filled. Devolvement and definition of budget can then proceed and at the same time the director and service manager must consult with each group of staff being brought into the integrated department, outlining their philosophy, plans, timescale, and managerial structure and honestly addressing the anxieties which will be raised. It is important not to prolong this stage any further than is absolutely necessary because of the escalation of anxiety which occurs during periods of uncertainty and change.

Creation of an action plan with realistic deadlines is an essential early step within the new department. It makes a constructive focus and conveys the message that this is a department of progress which is willing to tackle the gaps and inefficiencies of the past. By formally reviewing this action plan at frequent intervals (for example, every six months at first) this positive feeling can be maintained and the ownership of the whole child health service can be felt by all its parts. This builds confidence and morale which is in turn conveyed to those for whom the department was created—the children and their families.

1 Committee on Child Health Services. *Fit for the future* London: HMSO, 1976. (Court report.) (Cmnd 6680)

2 Hogg C, Rodin J *National Association for the Welfare of Children in Hospital Quality Review Setting standards for children in health care*. London, NAWCH, 1989.

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TYPES OF PSYCHIATRIC TREATMENT

Consultative work in child and adolescent psychiatry

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This is the ninth of a series of articles on treatment of child psychiatric disorders

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It should be said at the outset in a paper in a series on treatment that, of course, consultation is not a form of therapy. Indeed, in some important ways it can be seen as, at times, an alternative to therapy.

For historic reasons, because of the nature of the problems with which we deal, and because of the relatively ill defined (and perhaps undefinable) boundaries to our professional territory, psychiatrists are approached about a much wider range of problems than are attributable to psychiatric disorder, or which need psychiatric care. Every seriously unhappy or misbehaving child *could* at least in principle be taken on by a child psychiatrist. This, however, would make no more sense than to say that the 'right' professional would be a psychologist, or psychotherapist, or family therapist; or a paediatrician, general practitioner, health visitor, or counsellor with the appropriate skills and interests for that matter. (And there are some 30 or 40 other workers one could list.) It often isn't clear who is in the best position to help which child and family with whatever presents as a psychiatric problem. It depends not only on the clinical symptomatology, if any, but on the skills, strengths, availability, motivation, and interests of the other people involved with the child. This includes his or her parents and non-clinicians such as teachers.

Definitions

In this context the term consultation represents a set of techniques and approaches by which one professional can help another, not necessarily by taking over the child's case (although this can remain an option), but by seeing if he or she can help the first worker to manage the child's case after all. At the most basic descriptive level, consultation is about one professional (the consultant) helping another (the consultee) with a problem but without taking over care or professional responsibility. In this sense it differs from traditional *clinical* consultation, where the doctor sees and treats the patient. To avoid confusion I have recommended the term *interprofessional consultation*[1] for the work described here.

What is interesting about interprofessional consultation (and having thus identified it, I will revert to 'consultation' for short) is the complex range of implications of this relatively simple and straightforward definition. Consultation may involve, for example, a child psychiatrist and a paediatrician discussing a case in a way which leaves the referring professional feeling he or she would like to carry on with the patient concerned, and reasonably confident about doing so. In this example, the consultant may have helped the consultee appreciate what he or she can after all do for a child who was thought at first to need psychiatric care. But consultation can also involve a visiting doctor helping the staff of, for example, a school or children's home develop ways of handling a misbehaving boy effectively enough to avoid him having to be seen at a psychiatric clinic; and as a result, ideally, handling a proportion of other children more effectively too.

This may invite the question whether consultation is no more than a substitute for clear criteria for referral to a psychiatric clinic. However, while the criteria, say, for the referral of a child with the symptoms of meningitis or appendicitis from a generalist to a specialist are clear, decisions about when or whether people have reached the limits of their resources in handling unhappy, misbehaving, or otherwise malfunctioning children are less clear-cut. They bring in a whole set of other variables, such as ideas, imagination, problem solving skills, staff consistency and, not least, opportunities (or the lack of them) to get together and consider what to do in a reasonably calm, systematic, and focused way. It is a constant surprise in consultative work to find how frequently staff involved in child care can do more than they initially thought, when the only authority the outside consultant brings is 'permission to stand back for half an hour from the tension and hurly-burly of the work, and the skill to help them look again at what they are trying to do and how they are trying to do it.[1-3]

This implies a further important characteristic of consultative work: that the point is not for the consultant to bring his or her own methods and concepts to bear on the issue at hand, *but to seek to mobilise those of the consultees.* The psychiatrist consulting to, say, a paediatric clinic, school, or children's home doesn't try to treat the children 'through' the paediatrician, teachers or residential staff but uses consultative approaches to mobilise paediatric, teaching, and residential care experience and skill.

Of course, at first sight this may seem like a professional ploy akin to a jobbing gardener persuading his employer to do the digging, perhaps indicating that providing a better spade for the employer and a deckchair for the gardener might not come amiss. However, a central point in consultatation is that any of us may be able to manage a particular case or issue better than we initially supposed given a focused opportunity, encouragement, and help in what is essentially a problem solving exercise. If this works, and the admittedly limited research into consultation suggests that it can,[2–5] then the consultative process is an educational exercise as well as a way of handling day to day practical matters. Instead of being told what to do, shown what to do, or having the job taken over by someone who is supposedly more expert, the consultee learns something new. All of us, in our roles as teachers or trainees, know that this is an effective style of training, applicable to many (though not every) situation.

There is also an important reciprocity in the consultative relationship. The person who for this particular issue is the consultant does not take a superior stance, for example indicating that the other person should surely be able to work it out for himself. Rather, the joint exploration of what a colleague has indicated is a problem is a learning exercise for the consultant too. The outcome of, say, a surgeon consulting in this way with a physician should mean that each learns something about the other's work that they didn't know before. I would say that the most important single quality of a good consultant is curiosity; a genuine wish to find out what goes on in the other's field, the nature of the problems that arise, how they might be clarified, and how resolved.

The value of consultation

There are benefits of consultation that—potentially—make the whole exercise worth while. I say potentially because the field is relatively new, that is about 20 years from its inception, and needs more evaluative research. But on the face of it one can suggest the following advantages:

(1) As already indicated, it can be educational. If I set out to refer an anxiety-making diabetic adolescent to a physician and, instead, the physician helped me explore how I can help the adolescent and the family manage the diabetes more effectively and responsibly, then I would learn a great deal more than had the other doctor simply taken over. I might well find that I not only handle that patient's case better, but future cases too.

(2) Second, it may enable the patient to stay with the original practitioner instead of having another appointment with another clinician in another unit or hospital. How much time is taken up by patients in transit, or 'stacked' around clinics? This is not only a question of the convenience of those involved, but also concerns continuity of care, which is of particular importance in child and adolescent psychiatry, whether one is trying to ensure stability of relationships or the success of a behaviour therapy programme. (For example an autistic, unhappy, or misbehaving child is more likely to benefit from those in touch with them doing the right thing throughout the week, than from a psychiatrist doing something brilliant once a week in the clinic.)

(3) If it should emerge, immediately in consultation or later on, that the patient (or an aspect of care) would indeed be best taken over by the second professional worker, then the small amount of time 'lost' in consultation is likely to prove to have been well spent in clarifying the nature of the problem, who should be doing what, and (of special importance in the child psychiatry field) where appropriate authority for action (for example admission, medication) is going to come from. Certainly in 'emergencies' in adolescent psychiatry the gains can certainly outstrip the imagined problems when an admission to hospital, or an urgent and unplanned appointment, is held off for a little to allow for consultation between those already involved and those who are about to become involved.[6–9]

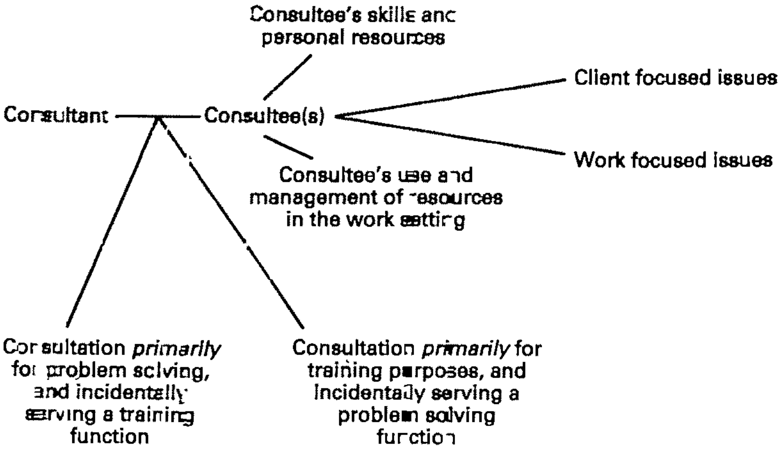
As was mentioned earlier, there are many different types of worker in the broad field of child care and mental and physical health. The field is kaleidoscopic. If the first professional approached (and this too is quite arbitrary—he or she may happen to be for example a teacher, a health visitor, a general practitioner, a paediatrician, a psychiatrist, a psychologist, or a counsellor, among others) feels out of his or her depth, it is often not absolutely clear to whom a rereferral should be made. If the art of good consultation were part of the professional repertoire of all such specialist workers, it might well be possible to make more economical and more speedy use of the immensely complex network we have of different types of skill and service.

(4) There is another value of consultation which I will refer to only briefly. So far I have suggested consultation as an effective way of problem solving and establishing the most appropriate help available. However, there is a great deal of ethical as well as technical controversy in medicine, and dilemmas for example about behaviour, education, social and family norms and expectations, HIV testing, genetic issues, high technology health care, alternative medicine, and sexual experience and behaviour which cannot be resolved by negotiation and information alone. The subjective views and the values of different practitioners, families, and indeed children themselves also need taking into account, and again the consultative process provides a forum for sorting out not only what is supposedly needed but what is wanted. Questions of the law relating to children[10] and of informed consent[11] can also be addressed in this way.

To sum up what is being presented as the value of consultation: in an increasingly complex, diverse, and changing field of need on the one hand and services on the other, consultation can be a more effective way than the traditional 'referral' of sorting out who is most able and willing to do what. And, further, it is a method which educates all sides as it proceeds.

The theoretical bases for consultation

Consultative approaches draw on a number of theoretical models. The figure suggests the various areas on which consultation might focus


Consultee's skills and personal resources
Consultant
Consultee(s)
Client focused issues
Work focused issues
Consultee's use and management of resources in the work setting
Consultation *primarily* for problem solving, and incidentally serving a training function
Consultation *primarily* for training purposes, and incidentally serving a problem solving function

Areas of work in consultation.

as the problem solving exercise proceeds. First, there is the relationship between consultant and consultee, so that the science and art of interpersonal relationships and interpersonal skills are involved. However, it is important to recognise that consultation is an equal relationship in which consultant and consultee contribute their respective understanding and skills to problem solving. It is essentially a joint exploration and negotiation, not about power but about how best to clarify an issue or problem and manage it.[1,2,4,7]

Second, there is the relationship between the consultee and the problem'. So far, this has been discussed in terms of a patient's problem, so this dimension of the figure is about clinical skills. We don't operate at peak efficiency all the time, especially when under pressure, and consultation, simply by creating a piece of focused space and time to take another look at a problem can enable us to use our clinical skills more effectively. Having said this, the question in hand is not invariably a clinical one; an organisational issue is also a legitimate subject to consult about, and again in the relative calm, it is to be hoped, of a consultation it is possible to look again at managerial, interprofessional, or other matters that need attention.

Thus far, then, consultation is described in terms of helping to mobilise personal skills. But another possible focus for consultative work is that which is available, or missing, in the work setting—for example facilities, personnel, and such basics as time (and timetabling) and space. It is interesting how often what may look at first like a clinical problem, or a problem of personal skills, can emerge as a primarily organisational problem.[1-3] The process of systematic joint inquiry about the precise nature of the problem, and precisely what is needed, can come up with some surprising results: that a child care team, for example, does not have effective support or supervision, or that a department has a chaotic timetable, conflicting goals, or confused decision making and communication systems.

Part of the interest and challenge of consultative work is that the process of objective, shared inquiry into precisely what impedes and what enhances work may well lead into unexpected areas, whose practical implications and conceptual roots may be in, for example, social science, ethics, anthropology, or politics.[1,9,11-13] This can cause problems, as is discussed below.

Practical aspects of consultation

Consultation may therefore be centred upon the consultee, that is in terms of thinking through and reviewing how he or she has been dealing with an issue, on a clinical or organisational issue the consultee identifies, or on the work setting. Of course, with mutual agreement, the focus can shift if that is appropriate.

Consultation has already been described as an activity where the style of problem solving leads also to further learning. It is important to note that further learning can also be the *primary* purpose of a piece of consultative work, for example if a child care team asks an outside consultant to help it develop its skills or the way it is organised, using day to day work issues as training material.

Consultation may be informal and *ad hoc*, for example a meeting over coffee, or in the way a referral or other inquiry is handled. It may involve two people, or a group, and may happen over a specific number of sessions or indefinitely.

Problems in consultation

(A) MISUNDERSTANDING

If it is consultation as described here that is being sought or offered, that should be made clear. For example, if the transfer of responsibility to another clinician, or the transfer of care from one unit or ward to another (the term 'disposal' is sometimes used) is wanted, it is annoying to be offered consultation instead. Such things happen, for example in intensive care areas.

(B) IS CONSULTATION TIME CONSUMING ?

The question is rather to do with whose time is consumed, and when. Writing a referral note to a clinic, where a patient and parents are booked into a clinic some weeks hence, may take just a few minutes in terms of staff time. A detailed clinical assessment, perhaps after a wait of several weeks, may use many hours and turn out to be not necessary. A consultative response to referrals, or at least to some of them, may actually save time, enabling a more finely modulated response (G Savoury *et al*, unpublished observations).[2,6,7] But it may not seem that way, and sometimes it may not be that way.

(C) CONSULTING AT THE WRONG LEVEL

It is an assumption of consultation that the consultee is at least potentially able, with help, to handle the matter in hand. However, if a problem looks like a clinical one (for example a registrar or staff nurse in difficulties over a case in an intensive care unit) but the answer lies in matters of policy (for example in terms of the medical or nursing training or supervision provided there), then the consultation will run into difficulties. Part of the skill of consultation is in checking that consultation is appropriate, with whom, and with what focus.

(D) STRAYING INTO OTHER TERRITORY

Consultation is something of a balancing act. It is not 'support', or psychotherapy, or supervision, or about intervening in local politics or administration, and yet approaches the edge of these areas. This is not simply a fine point of semantics. It is possible to get into real difficulty, and may be professionally and legally hazardous, if you believe you are offering consultation as defined here to a children's home, while the local authority believe you are supervising its staff. Such muddles happen.

(E) CONFIDENTIALITY

Confidentiality is sometimes an unexpected problem. For academic purposes it is easier to preserve the confidentiality of a patient than an institution and its staff. There is also the problem of the consultant being unhappy about, say, practices in a children's home, or problems in the staff, and finding that consultation is making no impact. The expectation of consultation that all participants are expected to be responsible, within their roles and levels of expertise, is a help here rather than a hindrance, because if consultees cannot learn from consultation there should be a mutual agreement to end it. Perhaps supervision is needed instead. If a consultant discovered serious malpractice the same would apply, and if none of the consultees were willing to explain it to the appropriate authority the consultant, in a different role, might have to instead.

(F) EXCESSIVE PURITY

Consultation needs to be reasonably clearly defined and its brief adhered to. At the same time it should be pragmatic and helpful, and should not become locked into a particular ideology. Thus the aim not to overlap with clinical work should not be used to defy common sense if, for example, a doctor consulting to the staff of a children's home or a school suspected that a misbehaving child had a psychiatric problem. If there is an impasse over this or any other sort of problem there is an in-built solution: consult the consultees and review what you are doing; it is all grist to the consultative mill. Moreover, consultative and clinical approaches can be explicitly used together in a dual consultative-diagnostic approach, in which tasks are shared out as, for example, those for the social worker, those for the parents, those for the school, those for the clinician, and indeed those for the child. This is particularly helpful in child and adolescent psychiatric practice, where 'who does what' can be contentious.[6–9, 11]

Conclusion

In child and adolescent psychiatry, and I would suggest in related fields too, it is often not obvious which professional worker is the most appropriate for which type of presenting problem. Moreover, it often happens that several people are needed to work together, sometimes on an *ad hoc* basis, for a particular child's case. I doubt whether this could ever be worked out as part of a 'grand design', or by computer. Consultation, as a collaborative skill all specialists could usefully have, offers a helpful way of clarifying who should do what with whom in a particular child's case, and it educates, and studies the field, as it proceeds.

This paper is based on a talk given to the Congress of the European Society for Paediatrics held in Athens in October 1990

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STATISTICS FROM THE INSIDE

7. Regression and correlation

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Some of the most important statistical analyses are those which deal with the *relationship* between a variate y and another quanitity x which is recorded on the same items. We may for example wish to relate the response to a drug (y) to the dose administered (x); or the head circumference of a baby (y) to its weight (x). A possible simple model for a relationship of this kind is to suppose that we can write

$$y=\alpha+\beta x+\varepsilon \qquad (1)$$

where the ε s are random quantities with mean zero.

To explore the implications of this, I shall need some notation. Suppose we consider all the items in the population which have a certain specific value of x, $x=x_0$ say. In our examples, these would be all the responses to a particular dose, or all the babies with a particular weight. These selected items constitute a population in their own right, a *subpopulation* as it is called. This subpopulation will have a mean value and this in general will depend upon which value of x we have chosen (mean response will depend upon dose, mean head circumference will depend upon weight).

A mathematician's term for a mean is 'expectation' or 'expected value' and the corresponding notation $E(y)$ is sometimes used to denote the population mean of y. Here for the mean of the subpopulation at $x=x_0$ I shall write $E(y|x=x_0)$ where the vertical bar should be read as 'given that', or in technical language 'conditional upon'. More simply, I can write $E(y|x_0)$. This mean value of a particular subpopulation is called a *conditional mean*, and in principle I can obtain the conditional mean of y for any given value of x.

Suppose now that I calculate the conditional means of y for a whole set of values of x and that I plot these means against their x's. Suppose too that when I do this the result is a straight line whose equation can be written as

$$E(y|x)=\alpha+\beta x \qquad (2)$$

This is just another way of writing the relationship (1) above. The relationship (2) is called a *regression equation*, and α and β are the *regression coefficients* The coefficient α is the *intercept*, that is the mean of the subpopulation at $x=0$, and the coefficient β is the *slope*, the amount by which the mean of y increases for a unit increase in x.

The regression equation (2) is only a partial description of the population of (x, y) pairs; it tells us the mean of the subpopulation at any particular value of x, but we still need to specify the variability and other properties. As well as a mean, each subpopulation will have a standard deviation and in the simplest case we assume that this standard deviation is constant and does not depend upon x. This standard deviation can be written as $\sigma_{y|x}$ to distinguish it from the *unconditional* standard deviation σ_y which applies to the whole population of y's ignoring the x's. It is sometimes useful in addition to assume that each of the subpopulations has a Normal distribution.

With these assumptions, the usual textbook formulas or computer programs can be used to obtain estimates *a* and *b* of α and β from sample data consisting of (x,y) pairs, and also an estimate $s_{y|x}$ of $\sigma_{y|x}$, the conditional standard deviation which measures the scatter of the y values around the regression line. From this, the standard errors of *a* and *b* can be obtained. Simple *t* tests can then be use to test hypotheses about α and β and to provide confidence intervals for them. For a reason to be clarified below, the degrees of freedom in these tests will be two less than the number of data pairs in the sample.

With regard to the x's, it is useful to distinguish two situations.

(1) Consider the example in which children are treated with one out of (say) four doses of a drug. What we have is a set of four subpopulations, and each subpopulation carries an x value which is a quantitative label—here, the dose. In this type of situtation, the x's are *not* random variables; if we think about drawing further samples of data, these will come from the same subpopulations with the same values of x. The x's are better described as values of a *variable* rather than of a variate.

(2) Now consider the other example, in which the head circumference of a baby (y) is regressed upon its weight (x). Now we have a *bivariate* population whose items are the babies and which has two variates recorded upon each item, head circumference and weight. Provided that our assumptions about the y's hold good, we can use exactly the same model for the regression of head circumference upon weight, embodied in equation (2), and we can estimate the parameters of the model using exactly the same methods. However, a new feature emerges. It is now quite reasonable to investigate another regression equation,

$$E(x|y)=\gamma+\delta y \qquad (3)$$

This is the regression of weight upon head circumference, which relates the conditional means of x to values of y. It is important to realise that this represents a quite different line from that given by equation (2). If we wish to know the average head circumference of a baby of a certain weight, then equation (2) with the coefficients α and β estimated from a sample will enable us to do so; if (for some reason) we wish to know the average weight of babies with a particular head circumference, the equation (3) must be used.

Suppose that we have a sample of (x, y) pairs and that from them we obtain the estimated version of equation (2),

$$\hat{y}=a+bx \qquad (3)$$

where $\hat{y}$ denotes the estimate of the conditional mean $E(y|x)$. For each actual pair of observations (x,y) we can calculate the residual $(y-\hat{y})$, the discrepancy between the observed value of y and the estimate of its mean. The estimate of the variance about the regression line, $s_y^2|_x$, is found by forming the sum of squares of the residuals and dividing this by its degrees of freedom. It can be shown that there are two exact relationships between the residuals—the sum of the residuals is exactly zero, and so is the sum of the residuals each multiplied by its value of x. This means that, if you are told all but two of the residuals (and all the x's), you can calculate the last two without looking at the data. This is why the degrees of freedom are two less than the sample size. The true conditional standard deviation $\sigma_y|_x$ is just the standard deviation of the true residuals $(y-E(y|x))$, and it and its estimate are often referred to as the *residual standard deviation*.

Calculating and using the residual standard deviation carries with it the assumption that the residuals constitute a random sample and exhibit no systematic features. Checking this assumption should be an important part of any regression investigation. The most useful checks are graphical. For example, a plot of the residuals against the values of x should show no exceptional features, such as outlying values or curvilinear trends.

A presentational point arises with the estimated regression equation (3) above. In this form, the intercept α represents the mean of the sub-population of y's at $x=0$. If x is a variable such as weight or stature this may be a quite meaningless quantity far outside the range of the actual data. As a result, the estimate a will be meaningless too, and because of the extrapolation it will have a very large standard error. It is preferable to express the equation in the form

$$\hat{y}=a+b\,(x-X) \qquad (4)$$

where X is a convenient round number somewhere near the centre of the data values. Note that this does not affect the value of the slope.

A situation that requires a good deal of care is that in which there are two levels of variation (see note 6 of this series), such as when repeated measurements of both x and y are made upon a number of subjects. Data of this kind are common when the investigation relates to the growth of children or the time course of the response to a drug. It will then be possible to calculate a regression line for each subject separately, describing the relationship of y to x within the subject, and an average of the within-subject slopes can be obtained. It will also be possible to calculate the means of x and y for each of the subjects and to estimate a between-subject regression based upon these means. It is important to realise that the within-subject and between-subject slopes will generally be quite different—they may not even have the same sign. It is possible, for example, to measure some quantity on a number of newborn babies and to calculate the regression of this quantity (as y) on gestational age (as x). But it is quite unsafe to assume that this between-subject regression can serve to describe what happens to a single fetus in utero as its gestational age increases.

Regression can often be a useful method of allowing for a factor whose effect upon the main variate of interest cannot be tightly controlled. As a simple example, suppose we wish to compare the head circumferences of male newborns with those of females. There is no great difficulty in obtaining samples from the two populations and the means can be compared by way of an unpaired t calculation. However, head circumference at birth is related to gestational age and it is unlikely that the two samples have exactly the same mean gestational age. Any difference that we observed between the two mean head circumferences may thus be in part a reflection of a difference in mean gestational age. Suppose then that we calculate the regression of head circumference (as y) on gestational age (as x) for each of the two groups. The two lines permit us to read off the mean head circumferences at a particular gestational age (perhaps 40 weeks), and these two conditional means can be compared by a modification of the usual t procedure. This technique has two advantages. Not only does it compensate for any imbalance between the gestational ages of the two samples, it also increases the precision of the comparison by utilising the standard deviations about the regression lines which will be smaller than those of the head circumferences considered in isolation. Note that the technique is most useful when the two lines are parallel; in this case the difference between the two conditional means will not depend upon the particular

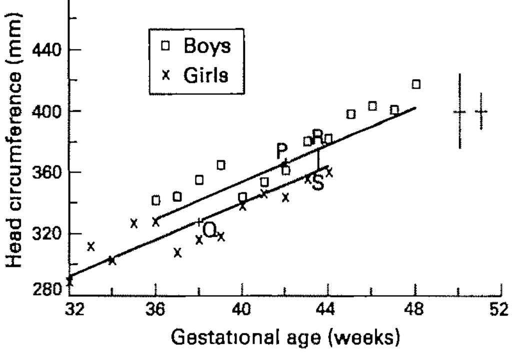

Figure 1 *Taken in isolation, the mean difference in head circumference between girls and boys is the vertical distance between the means P and Q. After adjustment for gestational age, the difference is that between the parallel regression lines, RS. The bars at the right of the diagram are twice the unconditional and conditional standard deviations*

x value that has been chosen. The parallelism of the regression lines can itself be tested by a straightforward t calculation using the standard errors of the two estimated slopes. This method is sometimes called an *analysis of covariance*, the quantity x being referred to as a *covariate*. I have illustrated it in fig 1, where I have for clarity exaggerated the difference between the x values in the two groups.

Closely linked to the idea of regression is that of *correlation*. Suppose that both x and y are random variables and let σ_y^2 be the variance of y ignoring the values of x and $\sigma_y^2|_x$ the conditional variance of the y's at a particular x value. Then the *correlation coefficient* ϱ is defined by the equation

$$\varrho^2 = 1 - \frac{\sigma_y^2|_x}{\sigma_y^2} \qquad (5)$$

with ϱ taking the same sign as the regression slope. This quantity is sometimes called the *Pearson* or *product-moment* correlation, to distinguish it from other similar quantities. There appears to be no good historical reason for adding the name of Bravais, as is sometimes done.

It can be seen that ϱ^2 is a measure of the information about y that is provided by a knowledge of x. Our uncertainty about a future value of y, considered in isolation, can be measured by the standard deviation σ_y or its square, the variance σ_y^2. If we are then told the corresponding value of x, the variance is reduced to $\sigma_y^2|_x$, so that the percentage reduction in variance due to the knowledge of the value of x is just $100\varrho^2$. Incidentally, this shows that ϱ^2 lies between 0 and 1 so that ϱ must lie in the range -1 to $+1$.

A point which is not made clear by this definition is that the correlation coefficient is symmetric as between y and x. This distinguishes it sharply from the regression coefficient and shows that correlation is only relevant when we are dealing with a bivariate population so that both x and y are random variables. We speak of the regression *of y on x* (or *of x* on y), but of the correlation *between* x and y.

The correlation coefficient is often described as a measure of the *association* between x and y, and this is true in the sense described above. It has to be stressed that it may be a rather misleading measure. Consider for example a correlation of 0·5—this is the correlation between the heights of fathers and their adult sons and sounds quite a high value. Yet knowledge of a father's height reduces the variance associated with his son's height by only $100 \times 0{\cdot}5^2 = 25\%$, and this translates into a reduction of no more than 13% in the standard deviation. In the same vein, the correlation coefficient vividly illustrates the difference between statistical significance and practical importance. With a sample of 50 (x,y) pairs, an estimated correlation of 0·35 is highly significantly differerent from zero, with $p<0{\cdot}01$; but a plot of some actual data points (fig 2) shows that this degree of association between the two variates is so weak as to be of little practical value in most circumstances.

It can be shown quite easily that the correlation coefficient, whether of the sample or the population, is equal to the geometric mean of the two regression slopes—in symbols, $\varrho = \sqrt{\beta_{y|x} \cdot \beta_{x|y}}$. It follows that the correlation is equal to zero only if the regression coefficients are equal to zero. The test of significance of the correlation coefficient against zero is thus exactly the same t test as would be used for either of the regression slopes, though as usual confidence limits are likely to be much more interesting than the result of the test in both instances.

The method of calculating confidence limits for a correlation coefficient, which can also be adapted to compare the values of two correlations, is of some general interest. A formula exists for the standard error of a sample correlation, but this is not useful for two reasons—the formula involves the unknown correlation, and in addition the distribution of the sample coefficient is liable to be far from Normal. This latter finding follows from the fact that the sample coefficient cannot go outside the range -1 to $+1$; thus if the true value of the correlation is (say) 0·8, the sample value can be considerably smaller than this but not very much larger (fig 3 shows the distribution for a true value of 0·8 and a sample of 20 pairs).

Both these difficulties can be avoided by *transforming* the sample coefficient (r, say) to a different mathematical form. The procedure involves two steps:

(1) Calculate $p = \frac{1}{2}(1+r)$. This quantity lies in the range 0 to 1.

(2) Calculate $z = \log\{p/(1-p)\}$ using 'natural' logarithms to the base e. This quantity is known as the *logit* of p and is unlimited in both directions.

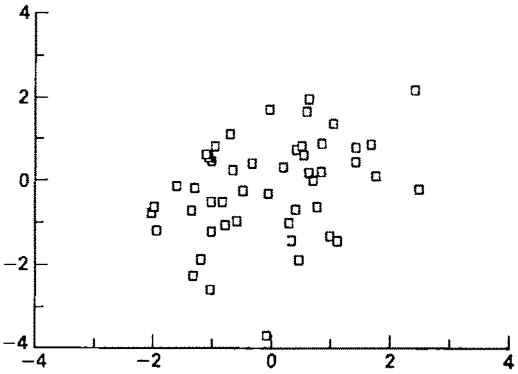

Figure 2 Data points with a correlation of 0·35 (p<0·01).

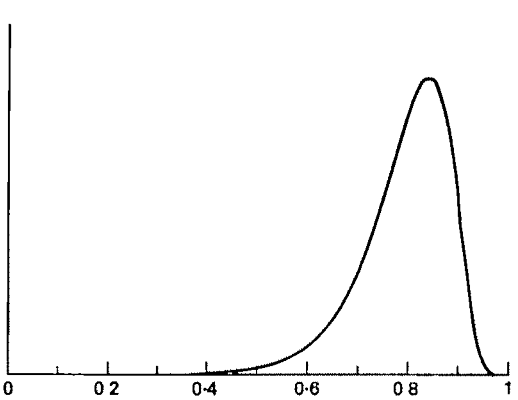

Figure 3 The distribution of the sample correlation coefficient, true value $\varrho=0{\cdot}8$, sample size 20.

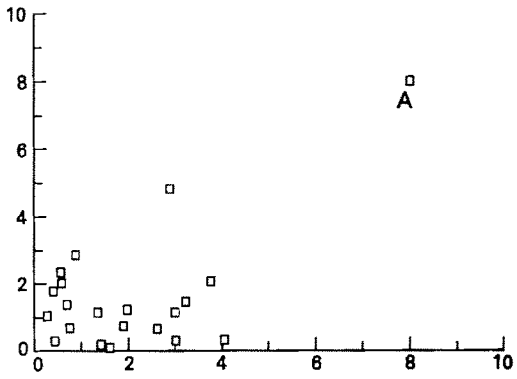

Figure 4 A sample with one outlying point.

It turns out that z is Normally distributed to a close approximation, with a standard deviation given by $\sqrt{4/(n-3)}$ where n is the sample size. Suppose then that we find a sample correlation of $r=+0{\cdot}8$ in a sample of 20 pairs. Then $p=0{\cdot}9$, $z=2{\cdot}197$ with a standard error of $\sqrt{4/17}=0{\cdot}485$. The 95% confidence limits for z are given by $2{\cdot}197\pm1{\cdot}96\times0{\cdot}485=1{\cdot}246$ to 3·148. These limits can be converted back to the correlation scale by calculating successively $p=e^z/(1+e^z)$ and $r=2p-1$. Corresponding to the limits 1·246 and 3·148, the values of p are 0·777 and 0·959, and the confidence limits for ρ are thus 0·553 to 0·918. This trick of transforming quantities to make them better behaved statistically is useful in many contexts, and I hope to return to it in a subsequent article.

For all its prominence in the textbooks, there are in fact rather few situations in clinical and laboratory medicine in which the correlation coefficient is a useful statistic. It is often quoted alongside the equation of a regression line, probably because it has been automatically provided by a computer program; but it is far more informative to provide the standard error of the slope and also the residual standard deviation which measures the variability of the data points about the fitted line. When x is an ordinary variable (such as the dose of a drug in a dose-response study) rather than a random variate, the correlation coefficient is usually not a meaningful quantity. It should also be noted that the correlation coefficient can be heavily influenced by the presence in a sample of one or two outlying points. Figure 4 illustrates this. As it stands, the sample there has a correlation of 0·61; but if the single point marked A is removed, this falls to no more than 0·02. As with most statistical analyses, a plot of the data is an almost essential part of the interpretive process.

One situation in which the correlation coefficient has no place whatsoever, and in which regression must be used with caution, is that in which two methods of measuring the same quantity are to be compared. The null hypothesis $\rho=0$ is obviously silly; nobody would suppose that two methods purporting to measure the same thing could be completely unrelated. If one method is a gold standard and the other a new technique, it may be of some interest to form the regression of the gold standard (as y) on the new technique (as x). The standard deviation about the regression line then provides information about the range of 'true' values which are consistent with a particular reading obtained by the new technique. Note however that for technical reasons the slope of the regression is *not* expected to be equal to 1·0, but to be rather less than this. A full discussion of the method comparison problem would take us too far afield at this point; a useful article is that by D G Altman and J M Bland, *Lancet* 1986;i:307–17.

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REGULAR REVIEW

Recent advances in understanding muscular dystrophy

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The isolation of the causative genes in the muscular dystrophies, and from these the identification of the defective protein products, is at last giving an insight into the molecular basis of these conditions. These advances have come about through the techniques of reverse genetics, or positional cloning.[1] All the muscular dystrophies have consistently eluded attempts to use standard biochemical techniques to identify the underlying defects in affected muscle. Most advances have been made in Duchenne and Becker muscular dystrophy, for which the gene and protein product have been known for some time.[2, 3] The gene for myotonic dystrophy has been isolated very recently,[4–6] and linkage analysis has identified chromosomal localisations for facioscapulohumeral dystrophy on 4q,[7] a form of recessive limb-girdle on 15q,[8] a form of dominant limb-girdle on 5q,[9] and Emery-Dreifuss muscular dystrophy at Xq28.[10]

The gene involved in Duchenne and Becker muscular dystrophy is the largest yet identified, comprising over 2·5 megabases of genomic DNA with at least 75 exons and some very large introns.[2, 11] This encodes a 14 kilobases mRNA, from which a previously unknown muscle protein, dystrophin, is translated. The predicted molecular weight of dystrophin is approximately 427 kilodaltons and it comprises about 0·001% of total muscle protein.[3] Dystrophin is also present in brain, where it uses a different promotor and exists as a different isoform.[12] It appears to be localised to neurons.[13] A protein with significant homology to dystrophin encoded by a gene on chromosome 6 has also been described.[14]

Study of the sequence of dystrophin suggests the presence of four district domains.[15] The N-terminal region has homology to α-actinin and appears to have a site of interaction with F-actin.[16] The second domain is thought to contain 24 or 25 triple helical repeats,[17, 18] which may confer elasticity on the molecule.[17] There follows a sequence relatively rich in cysteine residues and a C-terminus domain that is highly conserved between species.[19] Dystrophin has been shown by electron microscopy to be located at the internal cytoplasmic face of the plasma membrane[20] where it is associated with integral membrane glycoproteins[21] via its C-terminus domain. The structure of this glycoprotein complex has recently been described and it has been shown that dystrophin deficient fibres also show a reduction in some components of this complex.[22, 23] The structure and functional characteristics of the glycoprotein complex associated with dystrophin suggests that the function of dystrophin may be to link the sarcolemma membrane skeleton through a transmembrane complex to an extracellular glycoprotein which binds laminin.[22] It has been shown that dystrophin deficient fibres are more sensitive to hypo-osmotic shock than controls,[24] which supports the theory that dystrophin deficiency leads to mechanical weakening of the plasma membrane. An influx of calcium has been observed in dystrophin negative fibres, which may, directly or indirectly, stimulate protease activity,[25] and myotubes negative for dystrophin have been shown to have abnormal calcium ion channels.[26]

It is now known that most mutations in the dystrophin gene are deletions, which can be identified in approximately 65% of patients with Duchenne muscular dystrophy and up to 85% in Becker muscular dystrophy.[27, 28] The high frequency of deletions and in particular the tendency for deletions to cluster in two particular regions of the gene has not yet fully been explained.[29, 30] In those families where a patient has been shown to have a deletion DNA analysis offers a specific diagnostic test and a means of reliable and quick prenatal diagnosis. The demonstration of DNA abnormalities in patients without deletions is much more difficult in such a large gene, and only a handful of such mutations (point mutations and mutations in the promotor region) have been described.[31, 32] Techniques such as the use of dosage analysis for deletion detection in females, based on both Southern blotting and polymerase chain reaction (PCR) analysis, pulsed field gel electrophoresis, and most recently lymphocyte RNA PCR[33] have led to direct carrier detection being possible in some cases. However, in many cases carrier risk still has to be assessed as a probability calculation based on the results of creatine kinase testing and intragenic polymorphic markers. The high mutation rate in Duchenne muscular dystrophy has long been recognised, with approximately one third of cases estimated to result from a new mutation. The use of techniques that can directly detect a mutation in a boy and his mother has led to the recognition that germline mosaicism exists at a significant level in the Duchenne muscular dystrophy gene, with the risk of another affected son to a mother of an isolated case of Duchenne muscular dystrophy being around 20% with the at-risk haplotype even when a deletion has been identified in the boy and shown to be somatically absent in the mother.[34]

Dystrophin analysis, using antibodies to different parts of the dystrophin molecule, can be used both on muscle sections and western blots in diagnosis. Abnormalities of dystrophin seem to be specific to the Xp21 dystrophies, and so the finding of abnormal dystrophin can confirm the diagnosis even in the absence of a cDNA deletion.[35 36] The use of a combination of genetic and dystrophin analyses to distinguish Becker muscular dystrophy accurately from the often clinically similar conditions of spinal muscular atrophy and limb-girdle muscular dystrophy has allowed the prevalence of this condition to be reassessed, and it has been shown to be much commoner than had previously been thought,[37] the prevalence being similar to that of Duchenne muscular dystrophy and the cumulative birth incidence approximately one third. Some isolated cases of females with limb-girdle muscle weakness have been shown by dystrophin analysis to be manifesting carriers of dystrophin mutations[38] a finding of great significance in counselling these women. Dystrophin abnormalities do not seem to be so easily detectable in female carriers without symptoms.[39]

Studies of the gene and protein abnormalities in large numbers of patients are beginning to unravel the complexity of the relationship between genotype and phenotype in the Xp21 dystrophies. A range of clinical severity, from the classical Duchenne muscular dystrophy patients at one end to the relatively mild Becker muscular dystrophy patients at the other, with patients of 'intermediate' severity between, is now known to exist as a result of different mutations in this gene.[40] The ability to look directly for the molecular defect has also led to the recognition that severe muscle cramps may, at least for many years, be the only manifestation of Xp21 dystrophy.[41] Occasional asymptomatic cases have been recognised with dystrophin gene deletions.[42] The clinical range of severity is now known to be a reflection of a similar range of gene and protein defects. Deletions that disrupt the reading frame of the gene[43] (with the expected result that no recognisable protein could be produced beyond the position of the mutation), are often associated with undetectable dystrophin, and these patients are generally very severely affected. However, dystrophin is detected in some patients with out of frame deletions, and the size of this dystrophin implies that the deletion behaves as if 'in frame', that is recognisable dystrophin is produced right through to the C-terminus of the protein,[44 45] and the size of the protein is as predicted from the loss of the deleted exons.

Preliminary results suggest that the presence in muscle fibres of even a small amount of dystrophin may confer some functional advantage on these boys (LVB Nicholson, personal communication). At the other end of the clinical spectrum, patients with Becker muscular dystrophy are most commonly found to have deletions which do not disrupt the translational reading frame of the gene, so that a dystrophin molecule is produced which is internally deleted, but with both ends present and intact. Even very large deletions, providing they are in frame can be associated with a mild phenotype,[46] but it appears that deletions 45–47 and 45–48 of the dystrophin gene do tend to be associated with a relatively consistently mild clinical course.[28] Across the range of Xp21 dystrophy, increasing abundance of dystrophin does seem to be associated with a milder clinical course, but there is no one value for abundance which reliably predicts a particular phenotype.

It is likely that alternative splicing mechanisms around deletions at the RNA level may be more widespread in the dystrophin gene than has yet been described,[47] and this may account for apparent anomalies in phenotype-genotype correlations. Interactions with the dystrophin-associated glycoproteins or other genes may yet account for some of the unexplained variability in the dystrophin gene.

With an understanding of the molecular basis of the Xp21 dystrophies, work on possible therapeutic measures can now be more rationally planned and assessed. Animal models with dystrophin abnormalities have been identified.[48 49] Myoblast transfer and gene therapy using a 'mini-gene' construct have both shown some promising results in animal work,[50 51] and dystrophin transcripts have been identified in patients after myoblast transfer,[52] but widespread use of either technique in patients is still generally held to be a long way off.

The mutation responsible for myotonic dystrophy has recently been described.[4–6] There is variable amplification of a trinucleotide (CTG) repeat at the 3′ end of a gene, with an increase in the number of repeats associated with the disease phenotype. The number of repeats increases with the transmission of the mutation to successive generations. This mechanism explains the phenomenon of anticipation seen in families with myotonic dystrophy, where the severity of the disease is often seen to increase through successive generations. However, as amplification of the repeat may occur whether the mutation is passed through the male or female line, this mechanism is not enough alone to explain why congenital myotonic dystrophy is almost always maternally inherited. Women with myotonic dystrophy have around a 10% chance of having a child with congenital myotonic dystrophy, a risk which increases to 40% after the birth of one congenitally affected child, and which also rises with the severity of the disease in the mother.[53]

The gene has homology with genes encoding cyclic-AMP-dependent protein kinase, and its protein product has been designated myotonin protein kinase.[54] A 3 kilobase transcript is expressed at high levels in heart and lower levels in skeletal muscle and brain.[55]

Linkage analysis in the other muscular dystrophies should also ultimately lead to the identification of the genes and proteins involved, and no doubt to new ideas of how normal and abnormal genes and proteins interact in muscle. In the meantime, the work so far achieved has resulted in significant improvements in diagnosis and counselling for patients and their families.

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PERSONAL PRACTICE

Investigation of metabolic disorders resembling Reye's syndrome

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Abstract

Ten per cent of patients initially reported with Reye's syndrome in the British Isles (1981–91) were subsequently found to have an underlying inherited metabolic disorder (IMD). There was also evidence to suggest that other cases may not have been recognised. The range of metabolic disorders that mimic Reye's syndrome is wide and specialist, often complex, investigations are required to make a specific diagnosis. Those patients presenting with Reye's syndrome-like illness but also with one or more clinical features suggestive of an IMD require particular attention and detailed investigation. Recommendations for specimen collection and investigation are presented.

Reye's syndrome is a rare but serious disorder principally occurring in childhood, although adult cases have been described.[1 2] Essentially it is an encephalopathy complicated by hepatic dysfunction, although there is increasing metabolic derangement as the illness progresses. Although the precise aetiopathogenesis is unknown, it is clear that preceding (prodromal) viral infection together with aspirin consumption are risk factors for initiating the cascade of events that culminates in Reye's syndrome.[3] It is also believed that the fundamental site of the pathological process is the mitochondrion.[4]

It has become increasingly apparent that a significant number of patients who present with a Reye-like illness have an underlying inherited metabolic disorder (IMD).[5] An infant or child with an IMD, particularly one of the disorders of fatty acid oxidation, may be completely well for months or years until a stressful event (for example prolonged fasting, infection) triggers a metabolic crisis which can present as a Reye-like illness; sodium valproate treatment has also been associated with precipitation of the illness.[6] It is, therefore, essential that these patients are appropriately investigated, because there are implications both for management of the index case and for genetic counselling. For some IMDs prenatal diagnosis in future pregnancies and/or diagnosis in the neonatal period are available. Failure to investigate may be an important cause of misdiagnosis, especially in children under 3 years of age.[7]

We present our recommendations on which patients presenting with a Reye-like illness should be investigated for an IMD and on how to investigate.

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Classical Reye's syndrome—clinical presentation and definition

The 'classical' clinical picture of Reye's syndrome is as follows: a previously healthy child, aged about 7–9 years, acquires a viral infection, typically of the upper respiratory tract (especially influenza) or chickenpox. A few days elapse, and there may even be some recovery, but then the child becomes unwell with frequent, effortless, profuse vomiting. The conscious level may deteriorate and range from lethargy or drowsiness, through hyperexcitability and combativeness to deepening coma, often with convulsions. On admission, investigations will reveal increased hepatic transaminase (always), increased plasma ammonia concentration (usually), hypoglycaemia (in many cases, but not invariably), a prolonged prothrombin time (usually), normal plasma bilirubin concentration, and normal cerebrospinal fluid. There will be evidence of raised intracranial pressure and a liver biopsy specimen will reveal panlobular microvesicular fatty infiltration of hepatocytes with retention of nuclear position and no necrosis or inflammatory changes.

Electron microscopy of liver tissue will reveal ultrastructural changes, which are thought to be the only specific diagnostic markers of Reye's syndrome: proliferation of smooth endoplasmic reticulum, loss of glycogen, proliferation of peroxisomes and an alteration of hepatocyte mitochondria, including matrix expansion, loss of dense granules and the development of pleomorphic shapes. With progression to coma, these changes are accentuated. A population of clear cells appears, in which glycogen is diminished in granule size and in some cells is completely depleted. Mitochondria become large, with a progressively disrupted matrix. In children who survive 4–5 days after admission to hospital the liver injury appears to resolve, with restoration of glycogen stores and return of mitochondria to a normal appearance. Skeletal muscle shows abnormal lipid accumulation, glycogen depletion and mitochondrial injury in certain fibre types, but not all.[4]

The above description of a typical case embodies a range of both clinical and pathological features, the establishment of some of which, especially by electron microscopy, is constrained by the availability of technical resources and expertise within individual hospitals. For epidemiological surveillance purposes the case definition of Reye's syndrome has to be practical and simple and this inevitably compromises specificity for the sake of sensitivity. The definitions for Reye's syndrome used by the national surveillance schemes in the USA and in the British Isles are similar and the British one is as follows. A child under 16 years with unexplained non-inflammatory encephalopathy and one or more of:

(a) Serum hepatic transaminase increased $\geqslant \times 3$ upper limit of normal

(b) Plasma ammonia concentration increased $\geqslant \times 3$ upper limit of normal

(c) Characteristic fatty infiltration of liver (biopsy or necropsy).

Surveillance of Reye's syndrome

The British Reye's Syndrome Surveillance Scheme (BRSSS) began its activities in August 1981 and has now been maintaining a 'watching brief' over the occurrence of Reye's syndrome in the British Isles for just over 10 years.[3] It was a joint venture of the British Paediatric Association and the Public Health Laboratory Service Communicable Disease Surveillance Centre. The initial 'passive' method of reporting was enhanced in mid-1986 by transferring to the 'active' system of the British Paediatric Surveillance Unit (BPSU).[8] Cases who die are also ascertained via arrangements with the appropriate offices responsible for each of the constituent countries of the UK and the Republic of Ireland (British Isles): copies of all death entries in children under 16 years where Reye's syndrome is mentioned as a cause are supplied in confidence to the surveillance scheme.

Cases conforming to the criteria shown above are reported mainly by paediatricians, who are then invited to complete a questionnaire collecting detailed epidemiological and clinical information, or to send copies of summaries and/or necropsy reports. Clinicians are asked to inform the scheme if there is subsequently a diagnostic revision; information on such a revision is also actively sought by the scheme if there is concern about the validity of the diagnosis based on the initial information provided. Furthermore, general practitioners are contacted 6–12 months later to determine both outcome and whether the diagnosis has been changed.

Table 1 shows the annual total numbers of reports from 1981/2 to 1990/1; it also shows the numbers of patients who were subsequently ascertained as having had a diagnostic revision. After a peak of 93 total reports in 1983/4 there was a decline to a total of 25 in 1990/1, of whom 12 were subsequently reclassified.

Table 1 Reye's syndrome in the British Isles. Cases with follow up reported between 1 August 1981 and 31 July 1991

12 month period (August–July)	*Total reports British Isles*	*Classified as Reye's syndrome**		*Revised diagnosis (%)*
		No	*Rate†*	
1981/2	47	40	0·31	7 (15)
1982/3	69	59	0·46	10 (14)
1983/4	93	81	0·63	12 (13)
1984/5	64	56	0·41	8 (13)
1985/6	53	40	0·31	13 (25)
1986/7	47	26	0·20	21 (45)
1987/8	44	32	0·25	12 (27)
1988/9	31‡	18	0·14	12 (39)
1989/90	24‡	15	0·12	8 (33)
1990/1	25	13	0·11	12 (46)
Total	497	380		115

*Satisfied diagnostic criteria, diagnosis not revised.
†Per 100 000 <16 years of age.
‡Detailed information not available for one case.

Inherited metabolic disorders

The largest category of 'revised diagnoses' was IMDs—they accounted for over 40% of these cases (10% of total Reye's syndrome reports) and are detailed in table 2. This table also shows that three quarters of these were diagnosed in the most recent six years of the surveillance scheme. The commonest IMD identified was medium chain acyl coA dehydrogenase deficiency (MCAD). Organic acid disorders and urea cycle disorders were also significant groups.

There were nine patients in whom a metabolic disorder was strongly suspected (on clinical and biochemical grounds), but a definitive diagnosis was not reached. Of these nine, two had died and no investigations for an IMD had been undertaken but the diagnosis was suspected because of a history of a Reye-like illness in a sibling who had died. In one case there had been previous episodes of a Reye-like illness. Two patients died suddenly and unexpectedly in infancy and the diagnosis was suspected because of a fatty liver on histological examination, although material was not examined for an IMD. Three patients were undergoing detailed investigation because of clinical suspicion of an IMD: in two the results were not available at the time of reporting, whereas in the third the findings were not diagnostic of any known defect, although a disorder of β oxidation was suspected. There was no detailed information on the remaining case.

Among the six patients in table 2 with a suspected organic acid disorder, no detailed information beyond the initial abnormal findings in blood or urine which led the clinician to revise the diagnosis of Reye's syndrome, was available at the time of reporting.

The group 'classified as Reye's syndrome' (table 1) are those who are not known to have had a revision, although it is likely that they included

*Table 2 Revised diagnoses (Reye-like illnesses) 1981/2–1990/1 (1 August–31 July)**

	Total	
	1981/2–1990/1	*1985/6–1990/1*
Fatty acid oxidation defects (mainly MCAD)	20	17
Organic acid disorders	6	5
Propionic acidaemia	2	1
Ornithine transcarbamylase deficiency	5	1
Primary carnitine deficiency	1	1
Glutaric aciduria type II	1	—
Glycerol kinase deficiency	1	1
α_1-Antitrypsin deficiency	1	—
Fructose-1, 6-diphosphatase deficiency	1	1
Methylmalonic acidaemia	1	1
Pyruvate dehydrogenase deficiency	1	1
Ethylmalonic adipic aciduria	1	1
Inherited metabolic disorder (NS)†	9	7
	50	37

*Inherited metabolic disorders were the single biggest group (50/115=43%).
†NS=not specified—that is, strongly suspected clinically, but no definitive diagnosis.

some IMD cases—either because a late revision was not ascertained or because such a diagnosis was not sought by the clinician.

It is of concern that, although all the 'revised' and 'non-revised' patients met the basic case definition for Reye's syndrome, the opportunity to be reclassified was somewhat 'hit and miss', depending at least partly on diagnostic awareness and probably, in some cases, on availability of resources and access to expertise in diagnosing IMDs. Many in the 'non-revised' group were very young infants with atypical Reye's syndrome (for example no clear prodrome, minimal or no vomiting, very sudden onset) and some even had suggestive past medical or family histories (see table 3). There was another group who died suddenly and in whom the diagnostic label of Reye's syndrome was applied by the pathologist on the basis usually of liver histology but occasionally only on the macroscopic appearance of the liver. Sometimes the histology reports in these patients were not typical of Reye's syndrome (for example inflammatory changes or necrosis present, fat globules macrovesicular or eccentrically dispersed).

The BRSSS findings have highlighted the overlap between 'true' Reye's syndrome (the type of classical case described above and which is now only rarely occurring) and the 'metabolic masquerader'. They also suggest that there may be serious under diagnosis of these IMD among children presenting with Reye-like illnesses.

Investigation of children with Reye-like illness for IMDs

Although as yet no specific underlying metabolic abnormality has been identified in classical Reye's syndrome, the number of IMDs which could present with a Reye-like illness is large. It includes the disorders of organic acid metabolism, including fatty acid oxidation, and those of urea cycle, amino acid, and carbohydrate metabolism. There may be other disorders, for example defects of the electron transport chain which so far have not yet been reported to cause an Reye's syndrome-like illness. Many of these metabolic disorders mimic Reye's syndrome, not only clinically and biochemically, but also histologically.

For diagnosis of an IMD it is essential that appropriate specimens, especially urine and blood, are taken at the right time particularly if the infant/child is likely to die and that the case is discussed with the local clinical chemist. Without these important fluids, ideally collected premortem, tissue specimens taken at necropsy may be useless and a diagnosis may be missed.

Table 3 Features suggestive of an IMD in a child presenting with a Reye-like illness

The presence of *at least one* of the following should stimulate detailed and careful discussion of investigation for an IMD:

(1) Young age (<3 years) at onset of Reye-like illness
(2) Past history of: encephalopathic episodes; vomiting in association with viral infections; unexplained failure to thrive; neurodevelopmental disorder; 'near-miss' sudden infant death syndrome (SIDS)
(3) Family (both immediate and extended) history of: 'Reye's syndrome'; unexplained encephalopathy; SIDS
(4) Absence of history of a viral prodrome clearly separated from the onset of encephalopathy

WHO TO INVESTIGATE

The *possibility* of an IMD should be considered in *all* patients who present with a Reye-like illness. The presence of certain features (table 3) are particularly suggestive of an IMD and such cases demand careful investigation. Detailed discussions with a specialist centre providing investigations for metabolic disorders will be necessary.

Relevant history

Information which is particularly relevant to the investigation for an IMD includes:

(1) Family history—If previous siblings have died or had similar illnesses, what investigations were undertaken and with what results?

(2) Previous medical history—(i) Has this child been investigated for an IMD previously (for example because of a pre-existing neurodevelopmental problem)? If so, with what results? (ii) was the child receiving any drugs, particularly sodium valproate, before presentation with Reye's syndrome? (iii) has the child had any previous episodes of illness that were unexplained, for example hypoglycaemia, fits?

Current illness

Was the Reye's syndrome presentation precipitated by any change in diet/prolonged fasting or other stress associated event?

HOW TO INVESTIGATE

Patients with a Reye-like illness in whom a metabolic disorder is suspected are likely to have been investigated with a variety of first line biochemical tests. In addition to liver enzymes (aspartate aminotransferase or alanine aminotransferase, alkaline phosphatase, and γ-glutamyltransferase) these should have included: blood glucose, acid-base status, urinary ketones, plasma ammonia, blood lactate (if there is an unexplained metabolic acidosis).

Results of these investigations provide important clues to a possible metabolic disorder. Severe and/or unresolving metabolic acidosis, hypoglycaemia, hyperammonaemia, and lactic acidosis are all features of IMD, although not specific. At this stage the clinical chemistry laboratory should be asked to store deep frozen any surplus plasma or urine already collected and note the date and time of all specimens collected.

In *all cases* where one or more of the supporting features for investigation for an IMD (table 3) are present, specimens should be collected for additional investigations. If suitable specimens are not already available, further specimens should be collected *as soon as possible* after the onset of the illness (ideally blood should be taken before any intravenous infusions, epescially glucose, are given).

The investigations required are detailed below; results are required urgently as certain IMD diagnoses may indicate specific treatment regimens/courses of action. If the child is likely to die before definitive results from the blood or urine tests are available it is necessary to perform more rigorous sampling—either premortem or as soon as possible after death (table 4).

Initial specimens required

Initial specimens should if possible be collected before any intravenous treatment.

(1) Urine: ideally 5 ml but less is useful; this should be stored frozen (−20°C) as soon as possible (no preservative required).

(2) Blood: ideally 5 ml but minimum of 1 ml is useful if more cannot be obtained—place 1 ml into a fluoride bottle and the remainder into a heparinised bottle. Store both *plasma* specimens frozen (−20°C) and store packed red cells from the heparinised specimen deep frozen.

Investigations required

Investigations should be comprehensive to include all IMDs which could present in this way (table 5). Initial investigations should include:

(1) Urine: amino acids (qualitative) and organic acids by gas chromatography/mass spectrometry (essential to refer to a specialist centre).

(2) Plasma: amino acids (initially qualitative with quantitation if indicated).

In addition if there is *hypoglycaemia* a plasma sample (collected in fluoride) should be taken for 3-hydroxy butyrate, free fatty acids, and lactate. If there is a *metabolic acidosis* a plasma sample (collected in fluoride, table 4) should be taken for lactate.

Table 4 Emergency sampling requirements for biochemical analyses. If any of the specimens are taken after death, it is extremely important to record accurately both the time of death and when specimens were taken. Appropriate storage as detailed below is essential

Specimen type	*Specimen requirements*	*Storage*	*Comments*
Urine	5–10 ml; but less is useful. If the sample is contaminated with blood, centrifuge to remove cells before storage	Store at −20° C	If no urine is available consider bladder stab
Blood			
plasma	5 ml in lithium heparin and 1·0 ml in fluoride. Separate plasma as soon as possible	Store plasma at −20°C	Cardiac puncture may be necessary
whole blood	5 ml in EDTA (1–2 ml is useful) (Plastic tube for DNA studies)	Store as whole blood at −20°C	
Skin	*Sterility is of paramount importance.* About 2 mm cube (for detailed procedure, see Green and Insley.[9] Place in suitable transport medium (available from most virology or cytogenetic departments). In an emergency sterile isotonic saline can be used: *Do not use agar*	If necessary store at +4°C before despatch to laboratory: *Do not freeze*	Skin taken up to 24 hours postmortem is likely to be viable provided it is not infected
Tissues (liver, heart muscle, skeletal muscle)	Two or three needle biopsy specimens should be taken and immediately placed in a plastic tube (suitable for cryopreservation) and snap frozen in liquid nitrogen or solid carbon dioxide	Store frozen as cold as possible, preferably in liquid nitrogen or −70°C	Note: these specimens are for biochemical analyses only—appropriate fixed samples will be required for histology
Cerebrospinal fluid	1 ml clear fluid. If specimen is bloodstained, centrifuge and store supernatant	Store frozen (−20°C)	Cerebrospinal fluid useful for diagnosis of certain disorders—discuss with specialist laboratory

Table 5 Inherited disorders that may present as a Reye-like syndrome. (Note: This is not an exclusive list but includes those disorders that it is known may present as Reye's syndrome)

Disorders	*Supporting biochemical marker(s)*	*Diagnostic test(s)*
(A) Organic acid disorders: Propionic acidaemia Methylmalonic acidaemia	Metabolic acidosis Abnormal urine amino acids especially increased glycine. Profound ketonuria Note: significant hyperammonaemia and lactic acidosis can occur in these disorders	Urinary organic acids Fibroblast or tissue enzymes
(B) Fatty acid oxidation disorders (including disorders of carnitine transport)	Hypoglycaemia Absence of urinary ketones* Abnormal urinary organic acids† (for example dicarboxylic acids) Plasma carnitine abnormal (↑ or ↓) Plasma free fatty acid: 3-hydroxybutyrate ratio Notes: *positive ketones do not exclude these disorders; †can be normal	Fibroblast or tissue enzymes DNA studies
(C) Urea cycle disorders: Ornithine transcarbamylase deficiency (OTC)	Respiratory alkalosis,* Hyperammonaemia + + + Abnormal urine and plasma amino acids—especially increased glutamine and alanine Increased urinary orotic acid Note: *a metabolic acidosis does not exclude this disorder	Liver OTC DNA studies
(D) Disorders of pyruvate metabolism	Hypoglycaemia Lactic acid increased (urine, plasma, cerebrospinal fluid) Abnormal plasma and urinary amino acids—especially increased alanine	Tissue (liver/muscle) enzymes of pyruvate metabolism and electron transport chain DNA studies
(E) Carbohydrate disorders: Fructose–1, 6–diphosphatase deficiency	Metabolic acidosis Hypoglycaemia Lactic acidosis	Liver fructose–1, 6–diphosphatase deficiency

Additional tests may be required depending on results of the above investigations and therefore suitable samples, either as part of the initial specimen or as a repeat specimen, are required to be stored for this purpose. These include: plasma carnitine—1 ml heparinised plasma (total and esterified) stored deep frozen, urinary orotic acid—2 ml urine, stored deep frozen, and DNA analysis for MCAD defect —2 ml whole blood collected in EDTA and stored deep frozen.

INTERPRETATION

Investigation for IMDs requires considerable skill and expertise. In particular the definitive diagnosis of organic acid disorders can be very difficult even by those with considerable experience. It is unlikely that sufficient expertise is available at district level and reference to a regional/supraregional specialist centre is essential.*

Definitive diagnosis for many of these disorders requires enzyme measurement (usually in cultured skin fibroblasts/liver) or, more rarely, DNA analysis. This is particularly important for those families who would like the opportunity of prenatal diagnosis for subsequent pregnancies. For this reason it is essential to take appropriate tissue from the infant/child (table 4).

Discussion

The annual incidence of Reye's syndrome in the British Isles changed between 1981 and 1991 (table 1). The cause of this was probably multifactorial: the interval between 1981/2 and 1985/6 included the 'start-up' period of the surveillance scheme, when diagnostic and reporting awareness may initially have been low. The reason for the 1983/4 peak is unknown—it was not associated with any significant influenza activity that winter.

The steady decline in total reports from 1985/6 onward was almost certainly due, at least in part, to the public and professional warnings about aspirin in June 1986, followed by withdrawal of paediatric aspirin formulations and warning labelling on all aspirin containing products.[3] The decline particularly involved the classic cases of Reye's syndrome, an observation associated with a near halving of the median age of cases reported after 1986 compared to the earlier years.

Another possible cause of the decline in reported Reye's syndrome, particularly in recent years, was increased diagnostic awareness of the IMDs that mimic it and their recognition before the cases were reported.

It is likely that IMDs currently poorly defined or possibly new disorders will be described as causes of a Reye-like illness in the future. The importance of storing patient material (that is urine, plasma, whole blood, and tissues) from deceased cases who are strongly suspected of having an IMD, but in whom a definitive diagnosis has not be made, cannot be over emphasised.

The BRSSS data show that just under half (44%) of the patients who presented with a Reye-like illness between 1987 and 1991 were managed solely at their local district hospital and therefore there is a need for the general paediatrician and the local clinical chemist to be aware of the need for these specialist investigations, and to ensure appropriate specimen collection and storage. There is also a need for increased diagnostic awareness among pathologists—particularly those conducting post-mortem examinations on patients with sudden unexpected death in infancy. Dialogue with a specialist centre for the investigation of metabolic disorders is of paramount importance in all suspected cases.

Reye's syndrome is rare but undoubtedly cases of metabolic disorders are being under diagnosed as a consequence of inappropriate or inadequate investigation. The possibility of an IMD should be considered in *all* patients who present with a Reye-like illness, but particularly those who are of young age and/or have a positive past/family history.

Thanks are due to all BPSU respondents on whose goodwill the success of the reporting scheme depends, especially to those who reported patients with Reye's syndrome and provided detailed follow up information. The unit is funded by a grant from the Medical Research Fund of Children Nationwide. We also thank Lisa Newton for meticulous project administration.

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Archives of Disease in Childhood 1992; **67:** 1318–1320

LETTER TO THE EDITOR

Relationship between urinary and serum growth hormone and pubertal status

SIR,—We read with interest the paper by Crowne *et al* on the relationship between serum and urinary growth hormone concentrations during puberty.[1] As the authors pointed out we carried out very similar studies and came to very different conclusions. In our early studies of 24 normal children of both sexes over the full range of puberty stages we found very good correlation ($r=0·79$, $p<0·001$) between urinary growth hormone excretion and overnight mean plasma growth hormone concentration.[2] We have recently extended these studies comparing diabetic and normal adolescents and found the same correlation in both patient groups ($r=0·70$, $p<0·001$).[3]

Crowne *et al* suggest that the discrepancy between their study and ours could be explained by the fact that we studied mostly children in early puberty. In fact the predominance was in late (Tanner stages 3–5, n=15) rather than early puberty (stages 1–2, n=9). We have reanalysed our most recent results and still observe the same good correlation between urinary and plasma growth hormone in late ($r=0·69$, n=17) and early ($r=0·71$, n=19) puberty in both sexes.

The methodology for measurement of both urinary and plasma growth hormone concentrations was very similar in our studies and that of Crowne *et al*, and we believe that the important differences between the two studies are the collection methods and the way the urinary growth hormone data are presented. In the majority of their subjects Crowne *et al* used a 24 hour collection period with a 20 minute sampling interval for the serum profiles, whereas we used overnight collection with 15 minute blood sampling. The relationship between urinary growth hormone excretion and plasma growth hormone concentrations may not be constant throughout the 24 hours.

More importantly perhaps, Crowne *et al* reported urinary growth hormone excretion in relation to urinary creatinine excretion. Whereas this convention may be useful for checking the completeness of overnight urine collections, in this particular case it can be very misleading. We have examined overnight urine samples from 151 normal adolescents at different stages of puberty, and demonstrated that the urinary excretion of creatinine increases during puberty (see table). If urinary growth hormone excretion rates are expressed as a ratio of creatinine excretion therefore, it will be difficult to discern any increase of excretion of growth hormone during puberty, and any correlation which exists with plasma growth hormone concentrations will be lost. If a small group were studied over a limited range of puberty stages, this change in creatinine excretion would not be so significant, and indeed Crowne *et al* did present some data to support this position. In the subgroups of prepubertal children and in the group of six boys in early puberty, significant correlations were seen between urinary growth hormone excretion related to creatinine and mean serum growth hormone concentrations ($r=0·82$ and $r=0·74$ respectively).[1]

Mean (SEM) overnight urinary creatinine excretion (mmol/hour) in 151 normal adolescents. Figures in squared brackets indicate numbers of subjects at each puberty stage

Puberty stage	*Boys*	*Girls*	*Combined*
1	0·21 (0·02) [30]	0·22 (0·03) [7]	0·21 (0·02) [37]
2	0·28 (0·02) [25]	0·23 (0·03) [8]	0·27 (0·02) [33]
3	0·34 (0·03) [14]	0·42 (0·09) [23]	0·39 (0·05) [37]
4	0·37 (0·06) [8]	0·45 (0·05) [23]	0·39 (0·04) [31]
5	—	0·49 (0·04) [13]	0·49 (0·04) [13]

We believe that a note of caution should be added to the use of urinary creatinine ratios during puberty, and suggest that urinary growth hormone excretion should be expressed as a timed excretion rate without reference to creatinine. In our experience this does reflect overnight mean plasma growth hormone concentrations with some accuracy during normal puberty.

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Drs Crowne and Shalet comment:

We read the above letter with interest and thank the authors for their comments. In reply, although we reported our results as growth hormone: creatinine ratios, in line with other recent publications, we did also look at the correlation between total urinary growth hormone (uGH) excretion (pg/ml) and mean serum growth hormone. There was still no significant correlation between these parameters in the pubertal children, either in the total group (n=22) $r=-0·26$, p=0·24; group 1 (postcranial irradiation, n=14) $r=-0·02$, p=1·0; or group 2 (normals, n=8) $r=-0·4$, p=0·22.

Therefore the use of growth hormone: creatinine ratios cannot explain the different findings of the two studies. We feel that the inherent variability in uGH excretion in puberty as a result of changes in both growth hormone secretion and renal function must affect these correlations. The use of tightly defined subgroups of children in different pubertal stages may improve correlations between uGH and serum growth hormone but has implications for the establishment of normal ranges in pubertal children and therefore the use of uGH measurement in pubertal children with growth problems.

Neonatal BCG immunisation

SIR,—The annotation by Clarke and Rudd was a very helpful review of neonatal BCG immunisation.[1] However the technical difficulty of intradermal injections in newborn infants was not mentioned, although poor technique is likely to result in inadequate immunisation or avoidable local side effects.

The percutaneous multiple puncture technique, described over 30 years ago[2] appears to be both safe and effective.[3] The multiple puncture technique requires a more concentrated vaccine, suspended in dextran, and an adapted Heaf gun with a 20 G needle head. Any risk of the transmission of infection can be eliminated by the use of disposable magnetic heads for the Heaf gun.

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Malnutrition in children with cancer

SIR,—In their report of energy intake and basal metabolic rate in children with malignant disease receiving maintenance chemotherapy, Bond *et al*[1] refer to our work exploring the incidence of malnutrition in children with cancer.[2] They state that we found nutritional status to be generally adequate at diagnosis but to deteriorate as a result of treatment. In fact we found that nutritional status was frequently inadequate at diagnosis. This finding directly contrasts with nearly all other studies.[3 4] Our study of 48 newly diagnosed children with malignant solid tumours showed a marked discrepancy in the incidence of malnutrition assessed by conventional means when compared with arm anthropometry. Using conventional indices of weight for height, and height for age (as used by Bond *et al* themselves) only 7% of our patients were assessed as being malnourished at diagnosis. However, using arm anthropometry (mid upper arm circumference and triceps skinfold thickness) 27% of our patients were identified as malnourished. These conclusions were confirmed in a larger series of 100 newly diagnosed patients from our own institution that included children with leukaemia.[5] Attempts to assess energy intake at diagnosis suggested that a large number of patients (44%) were consuming considerably less energy both than the recommended daily allowance for their age, and estimates of their own previous 'normal' intakes. Children with intra-abdominal solid tumours were more likely to be malnourished at diagnosis (35%) than those with leukaemia (15%) or extra-abdominal solid tumours (7%). It is evident that the presence of a large tumour load in a young child (with or without ascites or pleural effusion) could have a significant influence on weight and weight for height, making this an unreliable index of nutritional status at diagnosis.

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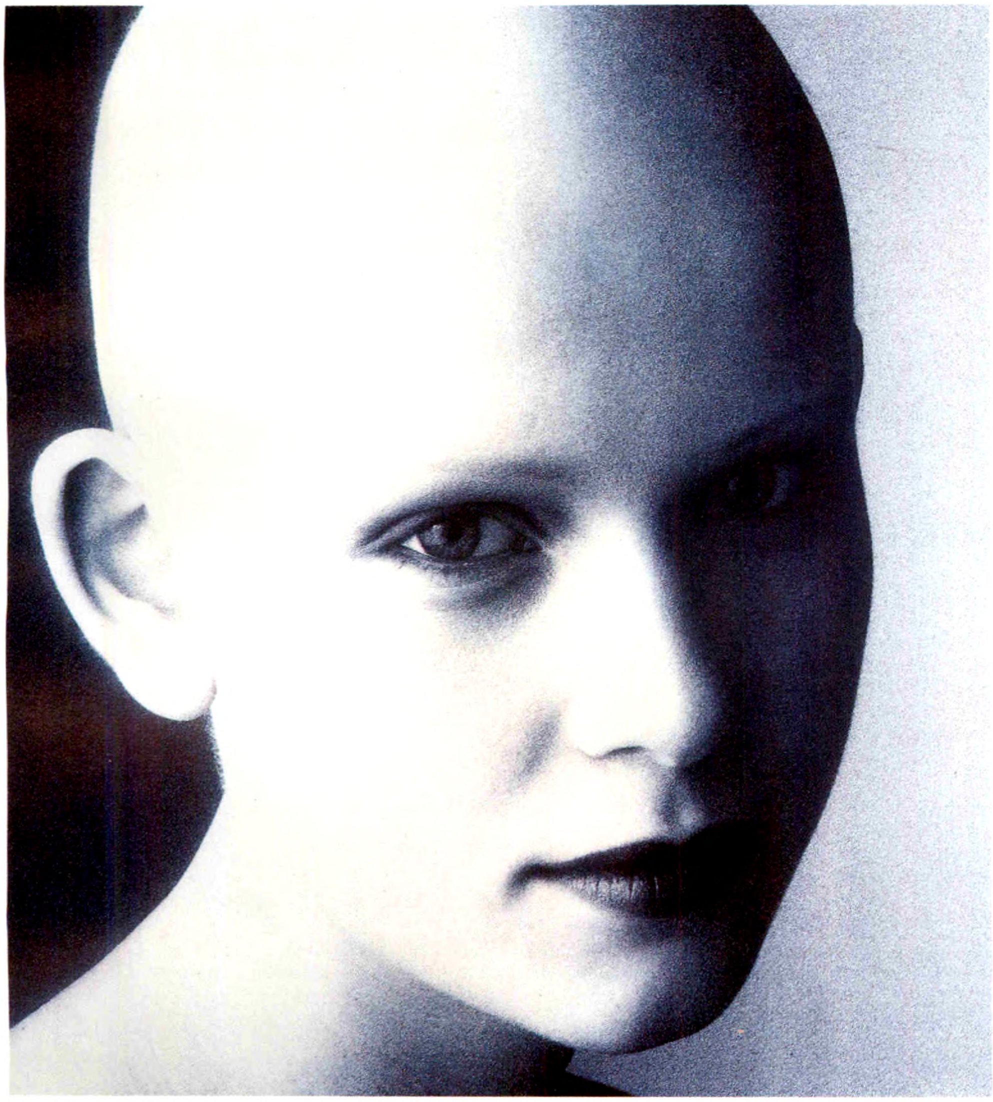

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We agree that treatment itself is likely to be an important factor in subsequent nutritional progress and in our study the prevalence of malnutrition, identified by arm anthropometry, rose to 46% over a median follow up period of 7·5 months.[2]

We conclude therefore that malnutrition in children with cancer is more common than generally recognised, particularly so at diagnosis, and that impaired energy intake is a factor in its causation. Further studies such as those by Bond and coworkers are required to explore the suggestion that changes in energy utilisation are also important, either at diagnosis or during treatment. Clinicians however must be aware of the greater incidence of malnutrition in these children and initiate appropriate strategies for nutritional support.[6]

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Rehabilitation and outcome after severe head injury

SIR,—The recent paper by Scott-Jupp *et al* is an important contribution to the subject of rehabilitation of head injured children.[1] It correctly highlights the inadequacy of present services including support and training for teachers who provide long term educational services.

We studied 220 children of whom half were followed up for three years after injury.[2] We found a substantial cognitive improvement between one and three years, a time when rehabilitation programmes have often ceased. Reporting on cognitive and behavioural problems at six months after severe injury must include many still in the early stages of recovery and before these cognitive gains have occurred.

In our study the relationship between length of coma and outcome is clear. Of 109 patients still comatose on transfer to rehabilitation (median 62 days) 48 remained completely dependent for all activities of daily living, against only one with partial dependency of 111 admitted conscious. The outcome in patients still comatose at three months and six months after injury was also found to be quite different.

Of interest is the fact that 87 (35%) of our children had a history of learning disorder or had shown attention deficit, impulsiveness, or emotional behavioural problems before injury. This would support the authors' impression that many of their children did have pre-existing problems placing them at increased risk for injury.

The data from Scott-Jupp *et al* is interesting,[1] but only a small number of children were followed up for a substantial time and the results must be interpreted with caution.

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1 Scott-Jupp R, Marlow N, Seddon N, Rosenbloom L. Rehabilitation and outcome after severe head injury. *Arch Dis Child* 1992; **67**:222–6.
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Paediatrics in the accident and emergency department

SIR,—I read the article by Phillips and Robson with interest.[1] The writers say that the Specialty Advisory Committee requires only three months paediatric experience before accreditation as a consultant. In 1974 when a working party was set up to discuss the training programmes for consultants in charge of emergency departments and the possibility of planning a programme for senior registrars, paediatrics was listed as being 'a minor specialty' and it was with the greatest difficulty that I managed to persuade other members of the working party that it was so important that a specific requirement of time should be included.

I agree that three months is not enough but I can assure you that to achieve even that was a considerable victory.

I have felt for a long time that community paediatricians could play a most useful part in accident and emergency departments where children are seen but which are not part of a children's hospital. Appointments that are linked between the hospitals and the community are valuable at junior levels and can be even more so at senior ones.

A properly run paediatric accident and emergency department can save money for a hospital by reducing the numbers of children who are admitted. This can apply with many types of problems. One example among many, in Sheffield, is that of the about 200 children who are seen each year with acutely painful hips, the majority are dealt with without admission.

Many *x* ray films, drugs, and unnecessary investigations can be avoided with benefit both to the child and to the finances of the hospital. A lot of problems, medical, surgical and social, can be recognised at an early stage and treated.

More children are brought to accident and emergency departments than to all outpatient departments put together—they deserve a service that is appropriate to their needs and to the needs of their parents.

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1 Phillips BM, Robson WJ. Paediatrics in the accident and emergency department. *Arch Dis Child* 1992;**67**:560–4.

Intravenous volume replacement: which fluid and why?

SIR,—Lucinda Huskisson has done well in her outline of the continuing debate on which fluid to use during resuscitation.[1] Doctors involved in the resuscitation of major trauma are now increasingly using the methodology of Advanced Trauma Life Support.[2] This concentrates on the first hour after trauma—the 'golden hour'—and presents a standardised approach to the management of trauma. With regard to fluid replacement, Hartmann's solution and blood are the only two fluids advocated. In the child a regimen of three challenges of 20 ml of Hartmann's solution per kg is advised followed by 10 ml per kg of blood if the patient is still unstable. Continuing instability as judged by cardiac status, conscious level, skin perfusion, and urine output should prompt definitive operative care. Paediatricians who find themselves involved in resuscitation in the accident and emergency department should be aware of this protocol as it serves to keep arguments over crystalloids and colloids out of the resuscitation room—as Dr Huskisson demonstrates by her 57 references that debate takes longer than a golden hour.

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1 Huskisson L. Intravenous volume replacement: which fluid and why? *Arch Dis Child* 1992;**67**: 649–53.
2 American College of Surgeons. *Advanced trauma life support*. Chicago: American College of Surgeons, 1989.

Sister journals

SIR,—David Mellor was undoubtedly right to criticise the English translations of the titles and abstracts of articles published in *Archives Françaises de Pédiatrie*.[1] Some of them were certainly inaccurate and/or clumsy. We have taken his comments to heart and retained a biomedical translator. Let us hope that he will soon have no cause for such comments.

Dr Mellor cannot understand why there are many fewer original articles and clinical reports in *Archives Françaises de Pédiatrie* than in *Archives of Disease in Childhood*. There are two very simple explanations. First, French paediatricians publish their best work in English language, mainly American, journals. Curiously, the dominance of English in the scientific world has led clinicians and researchers wanting to be sure that their work is known to publish in English. This is exacerbated by the tendency of granting bodies in France to give a priority to such publications.

Second, many of the subscribers to *Archives Françaises de Pédiatrie* are more interested in articles on new techniques, analyses, and applications than in research articles. This problem is not peculiar to French paediatrics; several other European journals have the same balance. The survival of our journal depends on the number of subscribers, and more and more of them do not want articles that are too research oriented or that deal with very rare conditions. This may be unfortunate, but it is the case.

The French, in common with other Europeans, probably have less difficulty reading and writing English than the English have in communicating in another language. We will continue to make an effort to communicate in English, as this provides a wide range of other benefits. The opening of the European common market may well be a good time for European paediatric journals to discuss the possibilities of better communications or even cooperation to avoid the 'arrogance' of one particular group trying to protect its own language. Lastly, Dr Mellor compared the April 1991 issues of the two journals. We do occasionally, perhaps not frequently enough, publish reviews of books that are sent to us.

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1 Mellor D H. Sister journals—France. *Arch Dis Child* 1991;66:1364.

AUTUMN BOOKS

Essential reference

Recently the library committee at our children's hospital made finances available for the purpose of a selection of books, to be housed in a suitably secure setting—books do have a habit of disappearing—yet be available for 24 hour reference to solve the inevitable problems of diagnosis, investigation and management, which seem to occur in the middle of the night. Having democratically sought the opinion of many of the medical staff (senior and junior) it was surprising how uniform were people's opinions on what made an 'essential reference book'; this article summarises these views.

For the junior doctor just starting in paediatrics, the ideal literary purchase is one describing what to do in every emergency situation. Treatments and trends change so quickly in medicine that an up to date reference is essential. Thus, *Paediatric Emergency Medicine* by M Grossman and R A Dieckmann (Lippincott 1991) came out top in this section, out voting *Paediatric Emergencies* (J A Black: Butterworth, 1987) and the still easily read *Paediatric Emergencies* by Tom Lissauer.

Another clearly practical handbook which received a lot of votes and will certainly have a place on our 'instant access' shelf (although many staff already have their own copy) was *A Paediatric Vade-Mecum*, edited by Jack Insley and most recently updated in 1990.

Chemical Pathology and the Sick Child, edited by B A Clayton and J M Round (Blackwell Scientific Publications, 1984) was the outright winner in the 'best book to explain why this child is hyponatraemic, has hyperammonaemia and seems moribund' section. Covering all aspects of chemical pathology from neonatal to pubertal problems, while it is not 'light reading' it is a very useful guide on when to investigate, how to investigate, and what the results mean. It allows you to sound as if you know why you are asking the poor 'on call' pathologist for yet another lactate concentration and might even stop you asking for one!

For a basic paediatric textbook, more for the quiet moments in the mess, when there is little else to do, the consensus of opinion (shared by previous contributors to this section) was for *Nelson Textbook of Pediatrics* (14th Ed, Saunders, 1991) in preference to the other standard works *Textbook of Paediatrics* (J Forfar and G C Arneil) or *Principles and Practice of Paediatrics* (F A Oski *et al*). As a reference to check whether the child in 'admissions' might really have Loeffler's syndrome (Nelson, page 909), it is undoubtedly very adequate, and earns its place in our emergency collection. However, even though it was more popular with junior staff than its British equivalents, for the premembership readers, I cannot help but worry that some of its transatlantic views might not be warmly greeted by the examiners of the Royal Colleges.

Having confronted the emergency, made a diagnosis, checked the chemical pathology, and organised the basis resuscitation, the next difficulty in management is deciding drug dosages when the pharmacy is closed. In the prescribing category, the most popular choice was undoubtedly the *Paediatric Formulary* (2nd Ed, 1990), produced by Lewisham and North Southwark Health Authority (Guy's Hospital to you and me), not as easy to carry in one's handbag/back pocket as the *Alder Hey Books of Paediatric Prescribing*, but generally felt to offer that little bit more.

At present we feel the books described will allow us to 'double check' most clinical conundrums and form the basis of our 'out of hours' emergency library. We are a children's hospital, but are frequently confronted with sick neonates, thus undoubtedly soon our collection will need to include a neonatal guide—here N R C Roberton's *Manual of Neonatal Intensive Care* is still very popular, but a *Handbook of Neonatal Intensive Care* (H L Halliday, G B McClure, and M Reid, 1989) and *A Neonatal Vade-Mecum* (P J Fleming, B D Speidel, and P M Dunn) are both compatible. Other suggestions for our 'emergency' library that received more than one vote and seem sensible, but financial restraints do not allow their purchase at present, include *Practical Genetic Counselling* by P S Harper (Butterworth, 1988), a very useful book to have on the ward or in the special care unit, answering many of the simpler counselling questions asked by parents, in addition to a malformation book. Here, *The Malformed Infant and Child* by R M Goodman and R J Gorlin (Oxford University Press), with its simple line drawings, was as popular as the well established *Smith's Recognisable Patterns of Human Malformation*. A dermatology book is very useful for any children's ward with a receiving room and essential for an accident and emergency department. *Essential Paediatric Dermatology* by J Verbov (Clinical Press Ltd, 1988) offers good quality colour illustrations for comparison and is easily read. *The Handbooks of Investigation in Children* series were reasonably popular—designed to tell you whom and how to investigate and what the results mean. This series now covers haematology, endocrinology, neurology, and renal medicine. Useful for day case investigations, we felt the previously mentioned *Chemical Pathology and the Sick Child* would suffice for our emergency shelf.

These views signify only the ideas of myself and colleagues in my hospital and as such are obviously not sacrosanct. However, I feel confident our 'emergency reference' books will be regularly consulted and hopefully will answer most of the diagnostic difficulties confronting us when the main library is closed.

GORDON GLADMAN
Senior registrar

10. Recent Advances in Paediatrics. Edited by T J David. (Pp 246; £22·50 paperback.) Churchill Livingstone, 1992. ISBN 0-443-04520-8.

'I have some news for you which you were not expecting'. This statement, taken out of context from a perceptive chapter on the management of Down's syndrome summarises a valuable extension to a well known series.

There are new insights into old favourites, Crohn's disease, the *bête noir* of district paediatrics; the managment of severe asthma—timely when many departments are subjecting their procedures to audit, and hypoglycaemia where we are invited to banish the diagnosis of asymptomatic hypoglycaemia. There is good advice on investigation but for the older child a firm statement on what constitutes the blood glucose concentration below which the tests should be performed would have been useful.

There are useful chapters on what for most of us are rare diseases, namely HIV infection and genetic disorders appropriate for bone marrow transplantation. Although some such disorders could present on a ward round tomorrow. The 'new genetics' is already having its effects on our practice and increasing knowledge of neonatal oxygen radical disease is set to change our neonatal protocols in the next five years.

There is purple prose telling the story of 'outlandish factitious disease'—another 'new' disorder. Do some of our most brittle diabetic youngsters fall into this category?

This book is written for the general paediatrician. It succeeds—every chapter is relevant. It variously criticises our practice, invites us to drop outdated concepts, updates flagging knowledge of the scientific basis of some diseases, and supports us against modern myths—as in the chapter on food additives.

It is hard to criticise. One assumes that there is a publisher's limit on size and hence content should be viewed in the context of current issues of importance and recent editions in the series. However, with the increasing dissolution of traditional boundaries between hospital and community there should be a place in each volume for primary and community child health topics. All chapters would benefit from the discipline of 'Key points for clinical practice' and 'Key questions for the future' would be thought provoking. Some of the physiology is a little hard going as in the description of oxygen free radicals and would have gained from further expansion.

However, these are small points in the context of a book which is a very valuable aid to our clinical practice and maintains the high quality established by its predecessors.

D THISTLETHWAITE
Consultant paediatrician

The Fetal and Neonatal Brain Stem—Developmental and Clinical Issues. Edited by M A Hanson. (Pp 289; £50 hardback.) Cambridge University Press, 1991. ISBN 0-521-38357-9.

The immature brain stem appears to have the major role in control of fetal breathing and its circulation, modulation of pain response, and the development of sleep-wake cycles and diurnal rhythms. The fetus and newborn brain stem therefore performs most of the function of the central nervous system with the higher centres coming on-line over the months after birth. It is clear that understanding the fetal and neonatal nervous system depends on an understanding of the function of the brain stem. This book, on that subject, grew out of a Physiological Society Symposium held in the Oxford University Department of Physiology in June 1989. The contributions appear to have been updated and the book covers a wide range of developmental neurology issues. The book contains 15 chapters each written by an expert in the field. The contributions review carefully the basic science and apply this wherever possible to the clinical situation. It is clear, however, that the jump from animal work (mainly lambs) to the human is a somewhat tenuous one but this is acknowledged in the test. The main clinically relevent areas are in the control of breathing and the obvious relevence this has to cot death. It is of interest that the effects of hypoxia on the brain stem vary considerably depending on the maturation of the structure and this is clearly important in the understanding of cot death.

This is such a good book and of such a consistently high standard that it is invidious to highlight any one chapter as outstanding. This book deserves to be read by all fetal medicine specialists and paediatricians interested in neurological development and I strongly recommend it.

MALCOLM I LEVENE
Professor of paediatrics

Congenital Perinatal and Neonatal Infections. Edited by Anne Greenough, John Osborne, and Sheena Sutherland. (Pp 245; £29·50 hardback). Churchill Livingstone, 1992. ISBN 0–443–04508–9.

Do we really need another book on congenital and neonatal infections, given that *Infectious Diseases of the Fetus and Newborn Infant* by Remington and Klein (W B Saunders) is one of the great reference textbooks? The two main weaknesses of Remington and Klein are that the book is not really helpful for practical, daily decision making in dealing with neonatal infections, and that it is not up to date in some of the more recently described infections. Greenough, Osborne, and Sutherland have produced a book which addresses the latter, though not the former, deficiency.

The introduction to this book states that it grew out of a working party on TORCH screening. Its main strength is certainly in the field of congenitally or perinatally acquired infections, particularly the newest ones. Where it is uneasy is in deciding the extent to which neonatal bacterial sepsis should be included.

There are four short, general introductory chapters on obstetric and paediatric aspects of congenital infections, techniques of prenatal diagnosis, and the laboratory. The remaining 16 chapters are devoted to reviews of individual organisms. In addition to the TORCH organisms (toxoplasma, rubella, cytomegalovirus, herpes simplex virus) there are chapters on *Chlamydia trachomatis*, enteroviruses, hepatitis B virus, varicella zoster virus, HIV, gonococcus, and syphilis. These are all short, pithy chapters which are clinically useful, but somewhat sparely referenced. There is an excellent chapter on human T cell leukaemia virus type I (HTLV-I) which contains information hard to find elsewhere and a useful summary on parvovirus B19 infections. Bacterial sepsis is confined to chapters on group B streptococcus, *Escherichia coli*, and listeria.

This book is extremely useful for dealing with congenital or perinatal infections if you know or have a strong idea of the organism responsible. It is less valuable for dealing with day to day problems with suspected sepsis, although to be fair this was never the book's original intention.

DAVID ISAACS
Associate professor in immunology and infectious diseases

Pediatric Pharmacology: Therapeutic Principles in Practice. Edited by Sumner J Yaffe and Jacob V Aranda. 2nd Ed. (Pp 663; £73 hardback.) W B Saunders Company, 1992. ISBN 0–7216–2971–7.

This is the second edition of a book which was first published in 1980. Coincidentally, a UK book—*Paediatric Therapeutics*, edited by Baltrop and Brueton—has been published this year. I have also reviewed that book and it is impossible to avoid comparisons. I commented that such textbooks cannot hope to be comprehensive and despite this new megaversion with 663 pages, 81 authors and 52 chapters, there are still obvious gaps. The only subjects which do not require a regular update are the general areas of pharmacokinetics, two compartment models, drug monitoring, etc. These are extensively covered in the 180 pages before an individual drug gets a mention.

I enjoyed the debate on the ethics of drug research in children and also the reference to the child being a therapeutic orphan. It is correct to be cautious with prescribing but children could be missing out on valuable drugs because the literature states 'insufficient information available to recommend its use in children'. I believe the trend to use drugs on a named patient basis will grow otherwise information will never become available. Ciprofloxacin and gangcyclovir are two such examples.

The clinical section on either the drug (for example gentamicin) or the condition (for example diabetes) was in part excellent, in part ordinary. The concise chapters were well referenced with, for example, 251 citations on fungal infections. Disappointingly, there were few more recent than 1988. It is always going to be the case in a changing world that the print is barely dry before a new drug is manufactured which is too recent to get a mention but is now the leader of the pack. Adenosine does not appear in the cardiac arrythmia section and surely there could have been a stop press section for surfactants. The neonatal section was otherwise quite detailed with a whole chapter devoted to the prevention of bronchopulmonary dysplasia by alternate day injections of vitamin A.

There were some interesting contrasts with UK therapeutics. Despite not suffering from the same pressure of litigation as the US, our prescribing is more conservative. For example, in the section on the gastrointestinal tract, it was demonstrated how effective metoclopramide and loperamide can be in a specific situation. We have an indoctrinated bias against the use of these drugs because of the well known side effects. This book reminds us of their potential benefits. Another group of drugs fashionable in the US and not in the UK is amphetamines for the hyperactive child. Reviewing their benefits makes me feel that, through excess caution, we can deprive our children and their families of genuine therapeutic benefits. In contrast the chapter on asthma made me feel that this was a hand out given to wheezy Klingons visiting the star ship Enterprise. Intal is a curiosity drug, theophyllines are first liners, and salbutamol does not feature. Subcutaneous epinephrine is still recommended for status asthmaticus.

Despite these reservations, it is a well written book and I feel a lot wiser having read it. I am not convinced that there is a market for a large text book of paediatric therapeutics, but for those interested, I would go for the UK version because the drugs will seem more familiar. With the money saved, another vade mecum can be bought to replace the one that's just disappeared from the ward.

J G BISSENDEN
Consultant paediatrician

Medical journalism. The Writer's Guide. Tim Albert. (Pp 111; £12·95 paperback.) Radcliffe Medical Press, 1992. ISBN 1–870905–28–8.

Why do so many doctors want to the writers? Worse still, why do so many think they *are* writers? Journalists may have fantasies about being surgeons but I doubt if they try to act them out in the editor's office or the Duchess of York's driveway or wherever it is they congregate.

None the less, the urge is there, as editors of medical journals know to their cost; whether it be the medical knight who believes his every word is sacrosanct or the professor of gene splitting who can put pen to paper only in the style of scientific ponderous.

Tim Albert's guide is a gem; I'm not surprised as he has an impressive track record in turning medical sows' ears (and boars, for that matter) into journalistic silk purses. Spawned by the *Guardian*, *World Medicine* (of blessed memory) and matured at *BMA News Review*, he is now—in the words of Michael O'Donnell's forword, 'widely recognised as the leading trainer in medical journalism . . .'

Albert takes the reader through five stages of writing a feature article: setting a brief, planning, research, writing, and revision. He describes how to get started, how to comprehend the wide market for medical writers, and how to work to deadlines and wordage limits.

There are lists of phrases to 'avoid like the plague' (such as avoid like the plague?) and pomposities are listed with their sensible alternate ('many' for 'considerable proportion', for example; perhaps a copy should go to 10 Downing Street for Christmas.)

Those who are natural writers may not ever have realised what they are doing but Albert points out that they use the active voice, are positive and use words which are simple, specific, suitable, and sensuous.

For the few who are venal rather than literary, he even tells us how to sell the finished product. Coping with rejection, subeditors, proofreading, and marking are all dealt with.

Just to show not all of his colleagues are reptiles, Albert quotes in full the code of ethics of the National Union of Journalists. Hands up all those who think he made it up in the bath? There is a useful glossary of journalistic jargon such as 'LUNCH: well-tested technique for gathering information, cultivating contacts and producing ideas. Not liked by accountants'. CONTACTS, incidentally, are a 'journalist's name for someone who will be useful to him. Not to be confused with FRIENDS'.

Whether you want to write for fun, for money, or even to impress editors of learned scientific journals, Albert's guide is a must. After all, if it results in just one acceptance it must be worth it—and its cost is probably tax deductible.

HARVEY MARCOVITCH
Consultant paediatrician

Significant Harm. Edited by Margaret Adcock, Richard White, and Anne Hollows. (Pp 155; £9·00 paperback.) Significant Publications, 1991. ISBN 0–9518761–0–4.

One of Wittgenstein's aphorisms (indeed, to be honest, the only one I can ever remember!) goes 'The meaning of a word is the way it is used'. This is particularly apposite in relation to the 1989 Children Act. The act stipulates that before certain action to protect children can be taken, the court must be satisfied on certain specific issues that appear in a checklist. Is the child suffering or likely to suffer harm if action is not taken? Is the child's health or development impaired? If the child has suffered harm, is it significant? Is the harm attributable to care given or likely to be given? How does the child's health and development compare with what could reasonably be expected of a similar child? Is the care given or likely to be given at a level that 'it would be reasonable to expect a parent to give'?

Now clearly all these terms require definition, and are likely to be interpreted in different ways. How bad does harm have to be before it is 'significant'? How likely is 'likely' —does this have to be a 30% chance or a 70% chance? What does one mean by 'a similar child?'. Does this mean a child with the same IQ and temperament or a child from a similar social class background? Do 'reasonable parents' beat their children, at times quite hard? Should one take ethnic status into account when making this judgment?

These matters of definition are already being tested in courts up and down the land. To help practitioners, paediatricians, psychiatrists, social workers, and others in their thinking on these matters, a group of experts drawn from the social work, medical, and legal professions who are involved in the preparation of training material before the act was implemented, have produced this manageably sized publication. I found it very helpful. Paediatricians are likely to find Margaret Lynch's chapter 'Significant harm: a paediatrician's contribution' particularly useful, but they will also find interesting Annie Lau's chapter on cultural and ethnic perceptions of the act and Arnon Bentovim's section that puts significant harm in a developmental and family context.

Most of us are likely to find ourselves in court giving evidence on these matters at some time. Anyone who wishes to reduce their adrenalin level by preparing for hostile questioning would do well to have consulted this book the evening beforehand.

PHILIP J GRAHAM
Professor of child psychiatry

Current Paediatric Practice. Edited by Peter Procopis and Geoff Kewley. (Pp 320; £25 paperback.) W B Saunders Company, 1991. ISBN 0–7295–0397–6.

Current Paediatric Practice is a compilation of almost 100 short and easily read reviews which have been collected over the last 10 years from *Clinical Bulletins* published in the Medical Journal of Australia and Australian Family Physician. The editors have brought together the contributions from a group of physicians and surgeons working at The Royal Alexandra Hospital for Children, Camperdown, Australia into a volume which spans the major areas of clinical paediatric practice.

The reviews, which vary in length from two to nine pages, are clearly laid out and are illustrated in black and white. The text is aimed at a wide audience and would interest paediatricians working for their MRCP, nurses who have an interest in paediatrics, and general practitioners looking for an easy to read review. The standard of the individual reviews is variable and as some were written up to 10 years ago their content is not always right up to date. Only a half of the reviews are referenced and in some areas such as haematology and endocrinology there is incomplete coverage of a number of common paediatric problems.

The reviews generally reflect the personal experience and practice of the reviewer and thus opinions may at times differ between the reader and reviewer about how to manage a particular problem. Although I have little disagreement with the accuracy of most of the reviews, I have difficulty in recommending either dilute carbonated drink or fruit cordial in the treatment of acute diarrhoea.

The reader should not expect state of the art clinical paediatrics in this book, more a chatty informal tutorial on a broad spectrum of paediatric problems.

W MICHAEL BISSET
Lecturer in child health

Lecture Notes on Paediatrics. 6th Ed. By S R Meadow and R W Smithells. (Pp 259; £12·95 paperback.) Blackwell Scientific Publications Ltd, 1991. ISBN 0–632–03113–1.

This paperback has recently undergone its sixth revision in 18 years reflecting the rapid growth and maturation of paediatrics as a specialty; the authors are to be congratulated on their efforts to keep it up to date. It is designed primarily for use by medical students and paediatric nursing staff, though junior paediatricians may find it of use.

Does it continue to be good enough to persuade the near destitute student to part with the meagre resource of his or her grant? The short answer is 'yes'. Although (as a Nottingham graduate raised on *Essential Paediatrics* by D Hull and D Johnston) the text was unfamiliar to me, I found it neatly laid out and sympathetically written. The first two chapters provide an excellent overview of child health and the third offers some sensitive advice and useful tips on how to examine children and escape with eardrums intact. Although the chapter on the newborn is clear and brief, I wonder whether, with the rapid expansion of neonatology as a specialty within paediatrics, it should be included in a text of this kind, particularly as there are several good concise neonatal handbooks available. The main factual content is covered in chapters dealing with problems by system, with information given in note form in short paragraphs. These have been updated and are well balanced.

There are some minor flaws. I was astonished that a picture of a child with hypothyroidism was titled simply 'A cretin' particularly as earlier chapters had stressed the merit of avoiding this way of referring to children. In addition, I feel that basic paediatric texts should draw attention to the existence of areas of controversy even though a full discussion may not be appropriate. The reader may otherwise fail to identify areas where controversy exists. An example of this is that many paediatricians would not embrace the concept espoused in this book of mandatory lumbar puncture in meningitis, and would consider the presence of papilloedema to be a clear contraindication.

In general then, a good first paediatric text book which is, by comparison with other medical texts, excellent value for money.

IAN MECROW
Senior paediatric registrar

Pediatric and Adolescent Gynecology. Edited by Sue Carpenter and John Rock. (Pp 493; Price $86·50 hardback.) Raven Press, 1992. ISBN 0–88167–839–2.

Some aspects of American medical practice and language do not translate well to this side of the Atlantic, and this book unfortunately provides numerous examples of such differences, which will inevitably reduce its appropriateness for the British bookshelf.

There is an irritatingly wide spectrum of styles in the book, with each chapter having different authors, and it is difficult to detect what readership the editors were intending to address. Some chapters are written at a very simplistic level appropriate for GCSE biology students, such as those on the menstrual cycle and on dysmenorrhoea (the latter with a remarkably enthusiastic recommendation for treatment with TENS, transcutaneous electrical nerve stimulation, more normally found in the north London National Childbirth Trust class than the teenage classroom!), while others are overloaded with heavyweight science and rarities, such as the 21 page chapter on 'Hirsutism in the Pediatric Patient' (with 179 references!).

There is considerable overlap and repetition (often mutually contradictory) between the chapters, which are frequently longwinded, such that one is not surprised to read the advice that it is necessary 'to allot one full hour' for the examination of a paediatric patient.

A particular difficulty for the British reader is the description in several early chapters of elaborate and intrusive techniques for the gynaecological examination of young girls, which are not practised in this country on adult women, let alone children. The use of the colposcope is advocated for routine examinations. The knee-chest position is described as ideal, with the alternative of labial traction to augment the supine position, neither of which are used in the United Kingdom. Data on transhymenal diameters are quoted religiously, although the wide normal ranges given serve to demonstrate why this isolated parameter is held, in this country, as being of limited use in the diagnosis of child sexual abuse. Perhaps, therefore, the most fortunate example of inconsistencies in content of different chapters is the much more measured view of the appropriate assessment of possible victims of child sexual abuse given in a later chapter. The last chapter, on the difficult topic of the gynaecological care of mentally handicapped children, is a notable inclusion.

On reflection, I would see this book as being available for reference in the hospital library, with the comprehensive chapters on vulval disease, vaginal discharge, abnormal bleeding, sexually transmitted disease, and tumours of the ovary, being useful for dipping in to. However, the trainee in gynaecology or paediatrics would need to be steered away from some of the more questionable approaches of other chapters, which serve only to demonstrate to the more experienced what wide differences exist in gynaecological practice on the two sides of the Atlantic.

SUSAN M TUCK
Consultant obstetrician and gynaecologist

Handedness and Developmental Disorder. By D V M Bishop. (Pp 208; £21 hardback.) Blackwell Scientific Publications Ltd, 1990. ISBN 0632-02842-4.

Is there any substance to the notion that autism and left handedness are related or that stuttering is a consequence of enforced right handedness? These, and the other controversies that are eloquently discussed in this book, have generated a good deal of heat over the last 60 years. Dorothy Bishop sheds some light.

The first half of the book guides us through the background to the subject. We are introduced to the motor learning and interference hypotheses for an advantage of handedness over ambidexterity—and we learn along the way that parrots show some left footedness and gorillas some right handedness. Other chapters discuss the relationship of handedness and cerebral lateralisation, genetic theories of handedness, and the normal early development of handedness in human infants. An excellent chapter covers the important issues of definition and measurement. Tests that measure direction of handedness and degree of handedness are compared. Validity, reliability, and sensitivity are lucidly discussed and we are shown how a strong hand preference on a handedness inventory can be consistent with a marginal advantage on proficiency testing and how strength of preference and consistency of preference may be confused.

Having demonstrated the anatomy and laid before us the instruments, Dr Bishop leads us, as it were, into the operating theatre. In the second half of the book, the evidence relating handedness and a variety of disorders—epilepsy, autism, Rett's syndrome, specific reading, and language disorders among others—is dissected. Paradox and contradiction are shown to arise variously from differences of definition, sample selection, measurement technique, and from conclusions that are not supported by the data presented. She discusses the role of publication bias in generating a momentum for associations that are in fact spurious. She concludes that much of the confusion could be resolved by an awareness of the methodological problems, a theoretical perspective that distinguishes different ways in which handedness and developmental disorder might be linked, and assessment procedures that are able to distinguish between such theories.

This book deals with a fascinating subject with wit and clarity. It is not for the bookshelf of the busy general paediatrician, but I would recommend it to those with a strong clinical or research commitment to the developmental disorders of children. It would also be valuable reading for any newly appointed clinical research fellow as the problems Dr Bishop identifies in handedness research have wider repercussions.

M PIKE
Consultant paediatric neurologist

The Stress of Multiple Births. Edited by David Harvey and Elizabeth Bryan. (Pp 140; £15 paperback.) Multiple Births Foundation, 1991. ISBN 0-9517709-0-X. (Available from the Multiple Births Foundation, Queen Charlotte's and Chelsea Hospital, Goldhawk Road, London W6 0XG.)

> 'Like babes in wombs . . . . .
> Urging slowly, surely forward,
> forming endless,
> And waiting ever more, forever
> more behind'.
>
> Walt Whitman—*Leaves of Grass*

Whitman captures in *Unseen Buds* a stress so often expressed by parents of multiple births. The feeling of the more having to be met by the less. What is so impressive about this collection of essays, is the 'more' understanding and thinking that is given to contain the stress of multiple births. The wealth of experience condensed in this incisive yet comprehensive collection of essays, will not only help and support those familiar with multiple births, but also the uninitiated. This book succeeds in raising our level of awareness of the stress surrounding this issue, and, in so doing, helps us to cope better with such stress.

The book is divided into five sections: antenatal, newborn, the early years, growing up as a twin, and higher multiple births. The collection of 13 essays starts with 'Obstetrical aspects of multiple births' by Ian MacGillivary, and ends with 'The long term outcome' by Ann Stewart. Pausing for thought along the journey with 'Ethical dilemmas' by Elizabeth Bryan *et al*, 'Family relationships' by Cherry Rowland, 'Twin relationships' by Stephen Isaacs and eight more interesting papers. The scope and content of the essays clearly meet their intentions.

The two editors, David Harvey of Queen Charlotte's and Elizabeth Bryan of the Multiple Births Foundation, are sensitive throughout to the fact that 'women least likely to want twins are those at greatest risk of conceiving them'. With their extensive experience they show the intricate interdependence between the physical, emotional, and financial stresses of multiple births. In conclusion, they suggest a number of resolutions (collected into three groups, that is counselling and support, infertility treatment and higher order births, and long term studies), to help professionals recognise the special problems concerned with the stress of multiple births.

ALAN LEVY
Principal child psychotherapist

Neonatal Clinical Pharmacology and Therapeutics. Edited by George Rylance, David Harvey, and Jacob Arando. (Pp 291; £50 hardback.) Butterworth-Heineman Ltd, 1991. ISBN 0-7506-1353-X.

This book arrived in my pigeonhole just as I was about to leave Cambridge for a walking holiday in Madeira. As a consequence I can vouch for the quality of the binding, which survived a week's battering in a rucksack, and the paper which possesses resistant properties to both water and alcohol. The text stood up better than most medical books to being read rapidly cover to cover like a novel. The editors have sought contributions from different expert authors writing 20 separate chapters and the topics covered include apnoea (Aranda), antibiotics (De Louvois), anticonvulsant therapy (Rylance), analgesia (Levitt), vitamin therapy (Wispe) in addition to a useful general revision of pharmacokinetics, the transfer of drugs across the placenta and into breast milk, and the effects of drugs taken by the mother both therapeutic and addictive.

There is much useful material in this book, although similar information could be found in recent review articles it is undoubtedly convenient to have the facts gathered together. Reference lists are adequate and as up to date as is possible in a textbook, although the same single case from a 1979 *Lancet* letter referring to the effects of maternal indomethacin appears in two successive chapters, and I found it surprising that I could not find any reference to the meta-analyses of maternal betamethasone and ritodrine. The book is far from being a comprehensive manual of neonatal therapeutics and there are significant omissions and some overlap. There is no material on chronic lung disease—no discussion of dexamethasone, bronchodilators, or diuretic therapy and nothing on pharmacological prophylaxis of periventricular haemorrhage. Blood transfusion is covered but there is no mention of the use of human albumin solution or immunoglobulin prophylaxis of infection.

The balance of the remaining material suffers both from an attempt to cover vast areas in a small number of words and from a failure to reflect the relative importance of the treatments described. Indomethacin treatment for patent ductus arteriosus merits only two pages, for example, whereas there is a considerable amount of space devoted to antiarrhythmic therapy. Reading the chapter on antibiotic therapy feels like a mental gallop through the field with no space allowed for advice regarding the treatment of specific infections. Similarly the chapters on total parenteral nutrition, hypoglycaemia, and transfusion therapy are too compressed to allow adequate discussion and left this reader feeling unfulfilled. The book does not contain an appendix with dosage regimens. The lack of specific therapeutic advice in several sections would make it unsuitable as the sole text to recommened to junior staff.

A good idea and a useful try, but perhaps not the first choice for any book tokens still lurking dog eared in the debris of one's wallet.

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Child Health—A textbook for the DCH. 2nd Ed. Edited by David Harvey and Ilya Kovar. (Pp 454; £32·50 paperback.) Churchill Livingstone, 1991. ISBN 0-443-04026-5.

Authors of a book intended to help candidates pass an examination have a hard task if the examination changes in content and this is the case with the DCH. In my view the second edition of *Child Health* has not kept up in reflecting the reform of the examination towards a problem orientated approach based on primary care presentation, with a greater content of developmental child health, and a health rather than disease emphasis.

Child Health is organised in a traditional way with its 29 contributors writing 34 chapters that mainly follow disease systems. There are useful additions at the end on 'ethical dilemmas' and 'examination techniques'. Twenty four of the authors are hospital based paediatricians and hence it is not surprising that the majority of chapters devote more space to secondary aspects of disease than to primary. For example, I could find no mention in the relevant chapters of developmental delay associated with iron deficiency; no mention of district handicap teams; no mention of common sleep disorders; little discussion on asthma management at school, and also inappropriate advice such as 'stool examinations should include culture' in the home management of diarrhoea.

There are also deficiencies in the 'preventive' chapters. There is scanty discussion on the format, content, and evaluation of a surveillance programme that now forms a central part of child health in general practice (though the hard to credit statement is made on p 56 that 'for most children, pre-school surveillance is undertaken in child health clinics organised by the child health services'). The increasingly recognised public health aspects of child health in relation, for example, to accident prevention receive no mention. The contraindications to pertussis given on p 38 are incorrect and do not detail the definition of a severe reaction (which is the only absolute contraindication). I have some carping comments about omissions, too—hyperactivity, the distraction hearing test, torticollis, and blocked tear ducts are not to be found in the book but all may crop up in the examination, and are important problems in clinical practice.

There is much to learn in the chapters on epidemiology by Stuart Logan, on child abuse by Jane Wynne with its clear illustrations, and on genetics by Sarah Bundey, which has valuable data on recurrence risks.

I very much hope that the editors will take a fresh look at the format of the book before the next edition to ensure that it is fully compatible with the reformed DCH.

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Handbook of Pediatric Imaging. Edited by Lori L Barr. (Pp 224; £80 hardback.) Churchill Livingstone, 1991. ISBN 0-443-08697-4.

'The *Handbook of Pediatric Imaging* guides the general radiologist through a thought provoking review of pediatric radiology'. This quotation from the preface provides a standard with which to compare this text.

In general, there is an uneven allocation of space to topics. It is a necessary editorial duty to control the enthusiasm of contributors for their special interests and to balance the content of the book.

There is a long contribution on dental radiology, mainly accurate and interesting, but out of proportion to other sections of wider interest. The pulmonary problems of the preterm infant receive less space and, due to the method of grouping by findings such as 'hypoaeration' and 'multiple cysts', some disease processes are described in several sections. The best description of pulmonary interstitial emphysema does not related to respiratory distress syndrome, but appears under a section headed 'Mediastinal air'.

This system is of value in preparing candidates for examination where clinical information may be lacking, but does not help with clinicoradiological correlation. In the bone section, Scheuermann's disease has three short and partly repetitive mentions, inaccurately recorded in the index.

In conclusion, this book is best used as a 'spot' primer for examinations: it is too uneven in content and style to be a major addition to the texts on paediatric radiology already available.

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Atlas of Rare Chest Diseases in Children. Edited by J Rudnik and R Kurzawa. (Pp 192; no price stated, hardback.) Rabka, Poland: National Institute of Mother and Child, 1990. ISBN 83-00-03293-2.

The National Research Institute of Mother and Child in Rabka, Poland have put together a collection of interesting rarities in this book. They have impressive facilities, but the atlas unfortunately reflects their lack of access to modern investigative resources such as computed tomography, magnetic resonance imaging, and fibreoptic bronchoscopy. Bronchograms are used in most of their cases, whereas we rarely perform one, and the contrast medium may soon be unavailable. The illustrations, although lavish, are often poorly reproduced, and the reference list has important gaps. In summary, an enviable collection of material, but it is difficult to know to whom to recommend this book for purchase.

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Correction

Early thrombocytopenia in HIV infection

We wish to clarify any ambiguity in this paper by R M Beattie *et al* published in September (pp 1093-4). In case 1, the last sentence of the second paragraph should read: 'He continued to receive this [intravenous immunoglobulin] every four weeks for six months'. In case 2, the third sentence of the third paragraph should read: 'He is currently on intravenous immunoglobulin every four weeks, daily zidovudine, and alternate day prednisolone'.

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Annotations

Silent gastro-oesophageal reflux: how much do we miss?

Gastro-oesophageal reflux in infancy is usually self evident and easily controlled. In most children, symptoms resolve by 18 months and only a minority develop oesophagitis, an iron deficiency anaemia, peptic oesophageal strictures, failure to thrive, or obstructive airways disease. Resolution is by no means lifelong, and many readers will not be surprised to learn that symptomatic reflux (heartburn) occurs daily in 7% of hospital medical staff, and at least monthly in 36%.[1] During the 1980s, interest in this disorder was given fresh impetus. First, by the availability of oesophageal pH monitoring, a more accurate method of diagnosis than a barium meal.[2] It is disappointing that despite its accuracy and ease of use,[3] it is still used by less than a quarter of paediatricians in the UK.[4] Secondly, a novel prokinetic agent, cisapride, became available and this was effective in controlling the symptoms of reflux and some of its complications.[5] It also became clear that in some children reflux was clinically silent and that this was potentially more of a problem than the child with frequent regurgitation. Two circumstances in particular spring to mind: (i) the infant with recurrent apnoeas, so called apparent life threatening events (ALTEs), in whom reflux is now recognised to be common and potentially fatal and (ii) the child with cerebral palsy, in whom there may be resistance to appropriate investigation and treatment.

Gastro-oesophageal reflux and ALTEs

Considerable uncertainty remains even about which system to investigate first when an infant presents with a history of ALTE and when clinical pointers are absent. The cause may be subtle and difficult to diagnose.[6] Up to three quarters of affected infants have pathological gastro-oesophageal reflux,[7 8] and it is therefore appropriate to address its importance in the pathogenesis of ALTEs. Reflux is more likely if the ALTE occurred while the infant was awake,[7] within two hours of a feed, or required vigorous stimulation by mouth to mouth resuscitation.[8] It is crucial to note that in infants with ALTE the presence of vomiting or frequent regurgitation is a poor guide to pathological reflux.[9 10]

For some time now the association between gastro-oesophageal reflux and ALTEs has been thought to be causal, partly because of the similarities in age and sex distribution between the two groups of affected infants. Until recently, firm proof of this association has been lacking. In part, this has been because of the lack of a close temporal relationship between reflux and apnoea. In a study of 24 infants with apnoea, or a history in a sibling of sudden infant death, it was not possible to show that a sudden fall in oesophageal pH, not necessarily below 4, induced central or obstructive apnoea, or vice versa.[11] None the less, reflux was present in all 12 subjects who showed obstructive pauses during sleep. In a study in which arterial oxygen saturation was monitored using pulse oximetry, episodes of arterial oxygen desaturation (to less than 90% for over 3 minutes) occurred within 4 minutes of a fall in oesophageal pH below 4 in the 14 subjects shown to have gastro-oesophageal reflux out a total group 16 infants with ALTE.[10] Pneumocardiograms were normal throughout. Infants with ALTE had a high incidence of reflux during sleep. The effect of oesophageal acidification on oxygen saturation was further assessed by administering apple juice (pH 3·5). While this had no effect on arterial saturation in controls, 50% of infants with ALTE demonstrated substantial acid induced decreases. Episodes of reflux occur more frequently in infants when awake than when asleep, although when episodes do occur during sleep they tend to be of longer duration. This is true both in infrequent episodes of physiological reflux and in infants with pathological reflux.[12] It now seems that the duration and not the frequency of these episodes during sleep may be an important determinant of both reflux associated respiratory disease and sudden infant death. Identification of those infants in whom gastro-oesophageal reflux is a significant contributory factor in their obstructive airways disease has long been a problem. In an early study it was suggested that the mean duration of reflux episodes during sleep provided the best separation between patients with and without reflux induced respiratory symptoms. Ninety four per cent of children whose respiratory symptoms ceased with control of reflux had a mean duration of sleep reflux of over 4 minutes, while all those with respiratory symptoms unrelated to reflux had a mean duration of less than this.[13] In a much larger recent follow up study, respiratory symptoms in over 500 children were classified as reflux or non-reflux induced on the basis of the respiratory response to successful antireflux treatment.[14] Despite the inherent difficulties in a retrospective analysis of this sort, and the recognition that reflux usually improves with time, all the children with respiratory symptoms unrelated to reflux had a mean duration of reflux episode during sleep of less than 3·8 minutes, whereas this was longer in 93% of the group with respiratory disease that was related to reflux. The same group have also examined the usefulness of this index in predicting sudden infant death in infants with gastro-oesophageal reflux. Nearly 500 infants under 6 months of age, of whom over half had a history of apnoea or choking, and who had undergone extended oesophageal pH recordings, were followed up and the cause of any deaths during the first year of life elicited. Of the 19 deaths, five were sudden infant deaths or due to a reflux induced arrest in hospital. All five had previously been shown to have pathological reflux, but they had also had prolonged reflux episodes during sleep.[15] Four out of the five infants had also had continuous reflux after an apple juice feed (so called type I reflux), a pattern of reflux associated with only a 21% chance of spontaneous resolution by 18 months.[16] Notably, the incidence of sudden infant death and reflux related deaths was lower after antireflux surgery (0/105) than after medical or no antireflux treatment (5/121). It therefore seems that the frequency of reflux during sleep is much less imporant than its duration, and may explain why some infants have infrequent but sometimes catastrophic episodes of reflux.

There remains the question of why some infants have such prolonged episodes of sleep reflux. Is there for example, an underlying difference in their sleep or in their ability to be roused by oesophageal acidification? Sondheimer and Hoddes have addressed this issue in infants with apnoea or chronic lung disease and were unable to show any differences in the pattern on electroencephalography during sleep between those infants with and without reflux.[12]

What can we conclude? Gastro-oesophageal reflux is certainly common in infants with ALTE and should be sought in them all, using extended oesophageal pH monitoring. Analysis should be directed at determining the duration of reflux episodes during sleep, rather than just relying upon more conventional indices such as the reflux index (percent of total observation time during which pH is less than 4). When found, reflux should be energetically treated with posturing, feed thickening, and cisapride, and oesophageal pH studies should be repeated to determine whether reflux is being prevented. In those infants who fail to respond, my threshold for surgical referral is now low, particularly as some infants will die within days of stopping medical treatment.[8]

Gastro-oesophageal reflux and apnoea in the preterm infant

Reflux in the preterm infant has been incriminated in apnoea, pulmonary aspiration, and bronchopulmonary dysplasia,[17,18] although accurate data on the incidence and severity of reflux in this population have not been available until recently. It is now clear that gastro-oesophageal reflux is common, and in some infants may be prolonged.[19] Nursing care is a notable precipitating factor and reflux is worsened by the administration of xanthines. In more mature, albeit prematurely born neonates, there does not appear to be a clear association between reflux and apnoeas.[20] Nevertheless, in preterm infants there is a subgroup with non-obstructive, xanthine resistant apnoea in whom reflux is particularly severe, and in whom treatment of reflux with posturing and feed thickening is associated with resolution of apnoeic symptoms.[19] The mechanism of this association remains obscure and the laryngeal chemoreflex[21] as well as lower oesophageal acidification may be important. However, the observation that resolution of apnoea does not occur as soon as reflux is controlled, but takes place over 48 hours, suggests that a vagally mediated reflex secondary to stimulation of laryngeal chemoreceptors by regurgitated milk is unlikely. It is possible that severe gastro-oesophageal reflux promotes apnoea by a vagally mediated reflex induced by oesophagitis and abnormal oesophageal motility.[22,23] Preterm infants are said to be at particularly high risk of gastro-oesophageal reflux and pulmonary aspiration during intermittent positive pressure ventilation.[24] Over one third of neonatal units in the UK avoid milk feeds during ventilation.[25] It seems likely that these risks may have been overestimated and that ventilation actually reduces rather than promotes reflux.[25] The use of positive end expiratory pressure and a consequent decrease in the reflux-promoting pressure gradient across the gastro-oesophageal junction may be important in this respect.[25]

Gastro-oesophageal reflux in children with central nervous system disease

Feeding difficulties, vomiting, and recurrent chest infections associated with poor growth and nutrition are common in children with central nervous system disorders, particularly cerebral palsy. It is increasingly recognised that gastro-oesophageal reflux plays an important part in generating many of these symptoms even though vomiting may be minimal. Using barium studies, Abrahams and Burkitt first reported a 75% incidence of reflux in a small group of children and adolescents with severe spastic cerebral palsy.[26] More recently, extended lower oesophageal pH monitoring has confirmed this association.[27,28] In some children gastro-oesophageal reflux may be the presenting symptom and will appear before the onset of overt neurological disorder.[27] In others, neurological diseases is apparent rather than real, and dystonic posturing, sometimes gross, is cured by effective antireflux surgery (Sandifer's syndrome).[29] Oesophageal motor dysfunction is common in children with psychomotor retardation. Lower oesophageal sphincter pressure is often low and peristalsis tends to be weak and disorganised.[28] Oesophagitis is common and may further contribute to oesophageal dysmotility, as well as cause severe anaemia. For this reason, oesophagoscopy is always worthwhile when oesophageal pH monitoring indicates severe reflux or when there is an iron deficiency anaemia. These children require energetic treatment of their reflux. It can cause severe pain,[30] which in older patients is often bad enough to be confused with myocardial infarction.[31] Medical treatment is often of limited value in these patients, presumably because of a primary disturbance in lower oesophageal acid clearance; in contrast to neurologically normal children, cisapride is disappointing.[32] Antireflux surgery therefore plays an important part, particularly in children with severe oesophagitis or other intractable complications. Many children will require preoperative nutritional support as profound protein energy malnutrition is common. At the Children's Hospital, Birmingham, the median weight for age SD score of children with reflux complicating cerebral palsy was −2·8, and nearly two thirds of the children had triceps skinfold thickness less than the 5th centile (unpublished observations). This may explain the increased perioperative mortality and complications reported in neurologically impaired children undergoing fundoplication.[33,34] None the less, it is important to point out that this experience has not been universal and other surgeons report zero mortality and very few complications.[35] Postoperatively, weight gain increases and time spent in hospital is reduced; the operation is highly popular with parents.[34,35]

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Excitatory amino acid neurotoxicity—a broader horizon for cerebral protection?

Substantial experimental evidence accumulated over the past decade indicates that an endogenous mechanism of toxicity, which results in a selective neuronal lesion more severe in dendrites than in axons (with sparing of glia), may be significant in the process of neuronal degeneration seen after brief neurological insults. Much of the evidence has been pharmacological with protection from the development of morphological neuronal injury by the use of antagonists acting specifically at the glutamate family of neuronal receptors.[1 2] The powerful protective effects of these antagonists are potentially of great clinical significance, and could have a role in the treatment of cerebral ischaemia, profound hypoglycaemia, and status epilepticus. In the immature brain, however, the potential usefulness of these agents may be precluded by their adverse effects on behaviour and brain development, because of the importance of excitatory neurotransmission in neuronal outgrowth, plasticity, and cell to cell interaction.[3] Despite such potential limitation for treatment, an understanding of the mechanism of excitatory amino acid neurotoxicity takes us significantly closer to conceptualising the process of neuronal death induced by acute insults, which must be central to any cerebral protective measures.

The 'excitotoxic' hypothesis

In its simplest form the so called 'excitotoxic' hypothesis of neuronal injury proposes that glutamate or other related endogenous excitatory neurotransmitters become toxic in their interaction with glutamate receptors, resulting in a cascade of intracellular events that culminate in neuronal death.[4–8] What makes an endogenous transmitter (which is normally released into and cleared from the synaptic cleft) become a neurotoxin is still a matter of much speculation, but these events may be attributable to:

(1) an excessive build up of extracellular glutamate because of abnormal neurotransmitter release, or abnormal uptake by neurons and glia;

(2) abnormal glutamate receptor activation because of abnormal postsynaptic sensitivity;

(3) abnormal induction and amplification of intracellular cytotoxic events.

Glutamate receptors

There is evidence for multiple subtypes of excitatory neurotransmitter receptors, which are commonly called glutamate receptors, as glutamate is the most widely accepted endogenous agonist. These receptors can be divided into three groups. There are two classes which possess an intrinsic ion channel, called ionotropic receptors. These are the *N*-methyl-D-aspartate (NMDA) receptor and the non-NMDA, kainate/quisqualate receptor, which are presumed to be large, multisubunit integral membrane protein complexes, which possess receptor binding sites with a central ion channel. The third class of receptor is the metabotropic glutamate receptor, which instead of possessing an intrinsic ion channel exerts its action through second messenger systems by activation of a G-protein.

An understanding of the extent to which these glutamate-receptor subtypes contribute to the neuronal injury induced by acute cerebral insults has been facilitated by experimental studies that have evaluated the relative neurotoxicity produced by intracerebral injection of specific receptor agonists, NMDA, quisqualate, and kainate. The results indicate major ontogenic alterations in the excitatory amino acid pathways, with different brain regions and neuronal types exhibiting their own developmental profile of susceptibility to each of the glutamate-receptor agonists. Comparing NMDA with non-NMDA agonists, on an equimolar basis, the greater degree of injury in the immature brain is produced by NMDA, and in the developed brain by non-NMDA agonists.[9–11] Furthermore, in the immature brain, there appears to be a transient overproduction of glutamate-receptor synaptic terminals, which may not only account for periods of heightened synaptic plasticity and consolidation of synaptic connections, but also provide a molecular substrate for increased susceptibility to particular insults.[3]

Glutamate-receptor antagonists

Of all the major classes of glutamate receptor, the best antagonists were first found for the NMDA receptor subtype. Consequently, most is known about the potential role of this receptor in mediating the neuronal injury of acute brain insults. It should, however, be remembered that many of the antagonists are not 'pure' in their differentiation between the receptor subtypes, particularly at higher concentrations, and so any beneficial effect may not be solely mediated by antagonism of a specific receptor subtype. In addition to the obvious interest in the pharmacologically 'designed' antagonists, which have for the time being only proved to be useful experimental tools, there has been some recent experimental[12 13] and clinical[14] interest in those agents already in clinical usage that have a known antagonistic effect on the NMDA receptor channel complex. These drugs are considerably less potent than the experimental agents, and include ketamine and dextromethorphan (phencyclidine site ligands) and magnesium.

Excitotoxicity and acute cerebral insults

Cerebral ischaemia, profound hypoglycaemia, and status epilepticus, result in a complex interaction between changes in cerebral energy metabolism, cerebral blood flow, blood-brain barrier function, neuronal depolarisation, and glial-neuronal interaction. As already mentioned, the main evidence that an excitotoxic mechanism provides a crucial link in the sequence of events leading to neuronal loss after these insults is pharmacological. Several studies have demonstrated that glutamate-receptor blockade can prevent neuronal injury induced by a variety of acute insults in both the mature and immature brain. Although the most well characterised insult is ischaemia, interaction at a single subtype of glutamate receptors cannot explain the findings in all the experimental models of hypoxic-ischaemic insult. As an example, it has been observed that there is a relative lack of neuroprotection with NMDA antagonists in some adult models of cerebral ischaemia.[15] These findings would be consistent with a model of glutamate-receptor mediated toxicity that takes into account the ontogenic profiles of neuronal injury due to exogenous glutamate-receptor agonists; ischaemia induced injury would be expected to be predominantly mediated by NMDA receptors in the immature brain and by non-NMDA receptors in the adult brain.

An excitotoxic process has also been implicated in profound hypoglycaemia and status epilepticus. In hypoglycaemia it seems likely that neurotoxicity is mediated by the NMDA receptor with aspartate as the endogenous agonist.[16 17] That glutamate-receptor antagonists are also potent anticonvulsants suggests involvement of these receptors in the mechanism of toxicity induced by status epilepticus. This speculative hypothesis, however, would be impossible to test with receptor antagonists, as blockade of glutamatergic neurotransmission for neuroprotection would also stop the epileptic activity. There has therefore been much effort in trying to demonstrate an abnormal accumulation of excitatory amino acids in the extracellular space during the period of insult.

The wider horizon for cerebral protection

This annotation has so far presented the barest model of excitatory amino acid neurotoxicity induced by acute cerebral insults, with the NMDA receptor providing a central role in the process of neuronal injury. Having illustrated some of the pharmacological evidence supporting the recent interest in the NMDA receptor, it is also worth noting that this receptor has unusual physiological properties. Because the receptor ion channel is blocked by normal concentrations of extracellular magnesium, the NMDA receptor is difficult to activate. Only as the membrane becomes depolarised and the magnesium blockade is lifted, can the receptor be activated. The ion channel then allows calcium to enter the cell. The resultant rise in cytosolic calcium is considered to be the initiating step in the cascade of intracellular events that culminate in neuronal death.[7 8]

The excitotoxic mechanism of neuronal injury has gained a broader interest beyond acute cerebral insults because of recent observations that indicate that neurons can be made more susceptible to the excitotoxic effects of glutamate and other related excitatory amino acids by manipulations of cellular energy metabolism and membrane potential.[18] It has been suggested that impairment of cellular energy metabolism leads to failure of the Na+/K+ ATPase that maintains the normal membrane potential, resulting in membrane depolarisation, reduced magnesium blockade, and easier activation of NMDA receptors.[18–20] The process of neuronal death could be initiated by impairment of cellular metabolism or membrane potential with an excitotoxic process being the final common pathway of neuronal death: an attractive hypothesis for chronic neurodegenerative disorders such as Huntington's disease and Parkinson's disease.

As our understanding of neuronal injury produced by excitatory amino acids has grown, experimenters have used glutamate receptor antagonists as pharmacological tools to explore the role of endogenously triggered excitotoxicity in the complex pathophysiology of brain injury following acute cerebral insults. Although the knowledge gained from such experimental models and tissue culture may ultimately be translated into practical clinical strategies for the treatment of acute brain injury, there is potentially a far wider application in chronic neurodegenerative disease, and some inherited metabolic disorders.

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ORIGINAL ARTICLES

Psychological effects of sodium valproate and carbamazepine in epilepsy

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Abstract

Information from standardised tests of intelligence, school attainments, attention, memory and visuomotor function, together with parent and teacher questionnaire information about various aspects of behaviour, was obtained for 63 schoolchildren with newly diagnosed epilepsy before treatment with sodium valproate or carbamazepine, and again at intervals for a total period of 12 months. The same information was collected on 47 matched controls. The children with epilepsy represented those under non-specialised paediatric care.

The result showed that both drugs were effective in most cases at modest dosage without causing notable psychological effects 12 months into treatment. Modest and temporary adverse cognitive effects seen earlier in treatment could have been the result of uncontrolled seizure discharge. Improved function was the same in children with epilepsy and controls. Some psychological abnormalities in the children with epilepsy were evident before treatment suggesting early unwanted effects of the epileptic process itself.

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The possible psychological effects of antiepileptic drugs have been studied since at least the 1950s but interest in this area of inquiry has increased considerably in the last 15 years or so, with published accounts about antiepileptic medications old and new. Of particular interest to paediatricians are the reports concerning sodium valproate and carbamazepine which, at least in the UK, have largely replaced phenobarbitone and phenytoin as the drugs of choice for treating epilepsy in children. Both these treatments have acquired the reputation of being effective in suppressing seizures, generally without causing harm unless given in very high dosage.

However, this reputation and, indeed, information about the psychological effects of other antiepileptic drugs, is mainly based on findings from studies of uncertain relevance to general, non-specialised paediatric practice (for review see Hirtz and Nelson[1]). Most investigations have been conducted on adult patients with complicated epilepsies or on normal adult volunteers. Patients studied have sometimes been taking multiple drug treatments or have been mixed regarding intellectual level and age, causing further difficulties in the interpretation of the findings. The psychological assessments employed have usually varied considerably from one study to another and have also frequently been questionable in other ways. Sometimes they have consisted of no more than impressions, and when laboratory (including computerised) measurements have been used, the relationship of such procedures to performance and behaviour in real life situations has not been demonstrated. Very few studies have established pretreatment baselines before assessing treatment over a sufficient period of time to allow possible short and long term effects to be detected. Other requirements not usually observed are the need in longitudinal studies of children to use carefully chosen controls in order to assess developmental influences and, as the effectiveness (or lack of it) of treatment on seizure occurrence may itself have psychological effects, the importance of taking seizure frequency into account over the period of study.

The present study was designed with these various issues in mind in order to make the findings and their implications for clinical practice easier to understand. The focus of the study was not children with epilepsy attending special epilepsy services but those under the care of their local paediatrician, and attending mainstream school. Therefore the children represented those with the more typical and milder forms of seizure disorder, taking treatment characteristically that employed within general non-specialist paediatric practice.

Methods

OVERALL DESIGN

This was a prospective study, over a 12 month period, in which repeated psychological assessments were made on a series of children with newly diagnosed epilepsy before the introduction of a single antiepileptic drug, and then repeated at intervals after the start of treatment. Regarding treatment effects, therefore, the children acted as their own controls over the course of the study. In addition, however, assessments were made of a group of matched non-epileptic children in order to assess practice effects on repeated testing, the effects of special attention given to them during the investigation, and developmental effects over the course of the study. Controls within the epilepsy group by matching for seizure frequency or abundance of seizure discharge were, or course, not possible because of the unpredictability of response to treatment and, in any case, the unfeasibility of trying to assess these seizure variables in this setting other than by ordinary clinical means.

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SUBJECTS

At our request paediatric colleagues notified us of children whom they had recently diagnosed as suffering from epilepsy and whom they intended to treat with sodium valproate or carbamazepine. For these purposes epilepsy implied the occurrence of at least two seizures of primary cerebral origin. Sixty three children were recruited who met the additional following criteria: (1) age between 7 and 12 years inclusive; (2) attending mainstream school with English as their first language; and (3) absence of gross neurological or psychiatric disorder, other serious chronic illness, or the need for long term treatment with other drugs.

These restrictions allowed psychological measurement to be kept uniform and possible confounding effects of low intelligence, cultural differences, or other serious disorder to be avoided. No attempt was made to influence the paediatricians' choice of antiepileptic drug treatment or any other aspect of management. All children with epilepsy remained exclusively under the care of their local paediatric service for the duration of the study.

A control group of non-epileptic children was identified as follows. As far as possible each child with epilepsy was matched with a non-epileptic child from the same class at school (to control for teacher differences and/or changes of teacher), of the same sex and age, and of the same overall attainments level as judged by the class teacher. Obvious differences in socio-economic background were avoided. The original intention was to match every child with epilepsy with a non-epileptic control but this proved impossible in 16 of the 63 cases mainly because parents did not want the school to know that their child had epilepsy, but also because a few schools were so small that a close match for sex, age, and attainment was not possible.

The parents of the patients for possible inclusion in the study and possible control children had been approached by letter with an explanation of the purpose and nature of the study and an invitation for their children to take part. Informed written consent was obtained from the parent or guardian of each child entered into the study. The study was approved by the local research ethics committee.

ASSESSMENTS

(1) Psychological assessments

These were carefully selected with the intention of covering a range of cognitive functions and behaviours. A combination was employed of formal testing of general intelligence and attainments, measures of specific cognitive abilities, and questionnaire ratings of behaviour by parents and teachers. All assessments were carried out by a psychologist experienced in working with children and their families.

Table 1 describes the *assessments of cognitive function* that were employed. These consisted of general tests and specific ability tests. The *general tests* were given before treatment was started and again at 12 months after the introduction of treatment. These tests were not considered sensitive to subtle psychological changes but were used to screen out children of low intelligence within the mainstream school population and to detect any gross changes of cognitive function over the 12 months period of the study. The *specific ability tests* were given before the start of treatment and at one, three, six, and 12 months after treatment had been introduced. They were designed to show possible drug effects and can be categorised as tasks involving aspects of attention, memory, and visuomotor function. These tests are described further in the appendix.

In a preliminary phase of the study, a number of specific ability tests were administered to normal children. Only those with minimal overlap with other measures and satisfactory test-retest reliability (shown in the appendix) were retained. The tests used were also designed to be enjoyable in order to prevent children dropping out of the testing sessions. The cognitive function tests were administered at the same time of day to each child with epilepsy and control child as far as possible.

The *measures of behaviour* that were used are listed in table 2. The Conners scales are well established and researched measures of a range of clinically important aspects of childhood behaviour. The cognitive function questionnaire was developed for use in studies of the behaviour at school of children with epilepsy. The derivation of this measure for use with teachers, and the aspects of behaviour at school, are very

Table 1 Tests of cognitive function

Test	*Functions assessed*
General tests	
Abbreviated form of WISC-R[2]	Verbal IQ, performance IQ, overall IQ*
Neale Analysis of Reading Ability[3]	Reading rate, accuracy and comprehension
British Ability Scale arithmetic test[4]	Arithmetic attainments
Specific ability tests (see appendix for further details)	
Cancelling test	Establishing an attentional set
Focal attention test	Focusing attention in presence of distracters
Sustained attention test	Maintaining attention during long monotonous task
Memory for stories	Memory beyond short term span for meaningful material
Pegboard	Visuomotor coordination
Digit symbol substitution test	Attention, visual search memory, and visuomotor coordination

[1] In this report subtest score findings are not described

Table 2 Measures of behaviour

Measure	*Behaviours assessed*
Conners Parents' Questionnaire (see Barkley[5])	Anxiety Conduct problems Impulsivity/hyperactivity Learning problems Psychosomatic problems Obsessionality Antisocial behaviour Restlessness/disorganisation
Conners Teacher Questionnaire (see Barkley[5])	Anxiety Conduct problems Inattention Overactivity
Cognitive Function Questionnaire[6] (for teachers)	Distractibility Drowsiness Fear of failure Memory Social isolation

different from that of the Conners teacher questionnaire.

From the information given in the published accounts of these assessments, they all appeared to be psychometrically acceptable. These measures were taken, in the case of children with epilepsy, before antiepileptic drug treatment was started and then repeated at one, three, six, and 12 months after treatment had begun. They were taken at the same point in time as far as possible for each child with epilepsy and control child.

(2) Assessment of seizure disorder and its treatment

Each epileptic child's type of seizure disorder was determined mainly on the basis of the clinical features of the attacks (as recorded by the paediatrician) and results of electroencephalography (EEG). Guidelines were provided to paediatricians emphasising the need for a detailed description of the attacks from the first subjective or objective change to the child's complete recovery, and the circumstances in which the attacks occurred. EEG assessment consisted of at least a standard recording (including overbreathing and photic stimulation phases) and in some cases a sleep deprivation/natural sleep recording. No structural cerebral lesion was detected in any of the children during the course of the study.

Seizure frequency was judged principally by means of a diary record completed each day by parents or other observers. Date, time, and type of attack was recorded in this way.

Table 3 Numbers of children in epilepsy and control groups according to treatment and sex

Sex	*Children with epilepsy*	*Sodium valproate*	*Carbamazepine*	*Controls*	*Total*
Boys	34	20	14	26	60
Girls	29	14	15	21	50
Total	63	34	29	47	110

Table 4 Mean ages (in years) of children with epilepsy and controls by treatment group and sex

Sex	*Children with epilepsy*	*Sodium valproate*	*Carbamazepine*	*Controls*	*Total*
Boys	9·68	9·68	9·67	10·10	9·86
Girls	10·02	10·67	9·41	10·08	10·05
All	9·83	10·09	9·54	10·09	9·94

Table 5 Types of seizure and drug prescribed

Seizure type (overall category)	*More specific seizure type*	*Sodium valproate*	*Carbamazepine*	*Total*
Absences		11	2	13
Other primary Generalised	Tonic-clonic	2	1	3
	Myoclonic	17	8	25
	Subtotal	19	9	28
Partial	Complex partial	2	5	7
	Benign centrotemporal	0	4	4
	Partial with secondary generalisation	1	7	8
	Uncertain type	0	2	2
	Subtotal	3	18	21
Unclassifiable		1	0	1
Total		34	29	63

Compliance with drug treatment prescriptions was assessed from the plasma drug level determinations made routinely in the paediatric outpatient clinics.

Any unwanted effects reported by the children with epilepsy or their parents were recorded by paediatricians to whom a list of possible adverse effects was provided by the investigators as a guide, although additional items were added to this list as necessary.

ANALYSIS

For analysis of the data the following groupings were used: all children with epilepsy on either sodium valproate or carbamazepine, children with epilepsy taking sodium valproate only, children with epilepsy taking carbamazepine only, non-epileptic control children, boys, and girls.

All pretreatment data was converted to adjusted means using covariate analysis where necessary to compensate for sex dependency. All results during treatment were calculated as percentage changes from pretreatment values for each group, using covariate analysis to correct for pretreatment differences between groups and any sex dependence.

Differences between control and treatment groups, the two treatment groups, and male and female groups were analysed using Students' *t* test. This test was also used to detect significant differences between the control group and the two drug groups separately.

In a few cases the first prescribed drug failed to change seizure frequency and the paediatrician then prescribed the other drug. In these cases, only data collected while the child was taking the first drug were analysed.

Results

(1) GENERAL CHARACTERISTICS OF THE GROUPS STUDIED

A total of 110 children were included in the study: 63 children with epilepsy and 47 controls. There were no withdrawals during the course of the investigation.

The numbers of children in the epilepsy and control group according to treatment and sex are shown in table 3. There were slightly more boys than girls on treatment and in the trial as a whole, but overall there were no significant differences regarding sex ratios. Table 4 shows the mean ages of the children, by treatment group and sex. Again, there were no statistically significant differences.

For the group of children with epilepsy, the types of seizure and prescribed drugs are shown in table 5. A wide range of seizure types was seen. In general, paediatricians had prescribed sodium valproate for primary generalised seizures (with the exception of two children with absence epilepsy for whom carbamazepine was used), whereas mainly carbamazepine had been prescribed for the treatment of partial seizures.

(2) COMPLIANCE AND SEIZURE CONTROL

Paediatric notes, including the results of plasma drug concentration determinations, indicated that no problems of compliance were encountered. The dosages used were modest: up to 30 mg/kg of body weight/day of sodium valproate, and up to 20 mg/kg of body weight/day of carbamazepine. These dosages gave plasma concentrations in the lower part of the 'therapeutic range' and achieved complete or almost complete control of seizures in 79·7% of patients, usually within the first three months of treatment, with no difference between sodium valproate and carbamazepine in this respect.

(3) UNWANTED DRUG EFFECTS

A total of 28 unwanted effects of antiepileptic drug treatment were recorded in the paediatric notes of 27 children. These are shown in table 6. Drowsiness was the most commonly reported problem and was described in four children from each drug treatment group. There was no report of intoxication or any serious adverse effect in any child.

Table 6 Unwanted drug effects

Side effect	*Sodium valproate*	*Carbamazepine*
Drowsiness	4	4
Weight increase	3	—
Diplopia	—	3
Rash	—	2
Nausea	2	—
Vomiting	1	1
Increased appetite	1	1
Ataxia	—	1
Abdominal pain	1	—
Hyperactive	1	—
Tremor	1	—
Headache	—	1
Gastric problem	—	1
Total	14	14

Table 7 Significantly poorer pretreatment scores on specific ability tests of each seizure type group compared with controls

Seizure type	*Test*
Absence (n=13)	Pegboard**
Other primary generalised (n=28)	Pegboard** Digit symbol*
Partial (n=21)	Cancelling* Focal attention* Pegboard* Digit symbol**

*p<0 05, **p<0 01.

(4) GENERAL TESTS OF INTELLIGENCE AND ATTAINMENTS

(a) Pretreatment

When the mean scores of all children in the study on the tests of general intelligence and educational attainments were calculated it was found that boys scored significantly higher than girls on the verbal and non-verbal intelligence quotient (IQ) sections of the Wechsler Intelligence Scale for Children—Revised (WISC-R) ($p<0·01$ in each case) and also obtained higher scores on the Neale reading rate and comprehension tests ($p<0·05$ in each case). These sex differences were taken into account by the use of covariate analysis when comparisons were made between epileptic and control groups.

No significant differences were seen in comparisons between the three overall categories of seizure type compared with each other and with controls. All these groups showed no significant difference from each other regarding mean age.

With the mean values adjusted by covariate analysis for sex differences, no significant differences were seen in comparisons between controls and any of the groups subsequently given antiepileptic drug treatment (sodium valproate, carbamazepine, either group) for WISC-R verbal or performance IQs, Neale reading ability scores or the British Ability Scales arithmetic score. This close correspondence demonstrated the accuracy with which teachers had matched epileptic children and their controls for educational attainments.

(b) After 12 months of drug treatment

No significant differences were seen in any comparison between any treatment group and controls for any of the measures of general intelligence or attainments.

(5) SPECIFIC ABILITY TESTS

(a) Pretreatment

No significant differences between boys and girls were seen in any of these tests.

Compared with controls, each overall seizure type group showed significantly poorer scores on various specific ability tests. These findings are summarised in table 7. Children with epilepsy consistently showed poorer visuomotor coordination irrespective of type of epilepsy, whereas aspects of attention were more characteristic of the partial group. In no test did children with epilepsy score significantly better than controls.

There were no significant differences between the different subsequently treated groups and controls.

(b) Changes during treatment

Table 8 shows tests on which one or other of the treatment groups were significantly different from the controls at each assessment after the introduction of antiepileptic drug treatment. In all instances the performance of the treatment group was worse than that of controls. In general, the sodium valproate and carbamazepine groups did not differ greatly in the few

Table 8 Differences in specific ability test results between each treatment group and controls for each time of assessment after introduction of treatment

Time of assessment after introduction of treatment (months)	*Treatment group (worse than controls in all cases)*	*Test*
1	Sodium valproate Carbamazepine	Focal attention** Pegboard*
3	Sodium valproate	Cancelling* Digit symbol*
	Carbamazepine	Pegboard*
6	Sodium valproate Carbamazepine	Digit symbol* Sustained attention*
12	Sodium valproate Carbamazepine	Focal attention* Sustained attention*

*p<0 05, **p<0 01

significant differences seen between each of them and controls. Attentional differences were more consistently seen throughout the repeated assessments, lower focal attention scores characterising the sodium valproate group and lower sustained attention scores the carbamazepine group. In addition, poorer performance than controls was seen in the pegboard measure of visuomotor coordination early in treatment with carbamazepine, and on the more complex digit symbol task during the middle phase of the 12 month period of treatment with sodium valproate.

(6) MEASURES OF BEHAVIOUR

(a) Pretreatment

No significant differences between boys and girls were seen on any of these measures. Table 9 shows the significant differences that were found between the different seizure type groups and control children. In all differences the epilepsy group score higher than controls.

Collectively, the children with epilepsy showed many significantly worse behaviours compared with controls. A common thread throughout was various aspects of poor attention and 'drowsiness' according to teachers, but in general the absence and partial seizure groups displayed a greater variety of disturbance than the other primary generalised group, sharing a higher level of impulsive/hyperactive and memory problems, as judged by teachers, compared with their controls. When the groups subsequently treated with sodium valproate or carbamazepine were compared with controls no significant pretreatment differences were seen.

Table 9 Pretreatment behavioural differences between each seizure type group and control children

Seizure type	*Questionnaire*	*Factor*
Absence (n=13)	Conners Parents' Questionnaire	Conduct problems* Impulsivity/hyperactivity** Learning problems* Muscular tension**
	Conners Teacher Questionnaire	Inattention*
	Cognitive Function Questionnaire	Distractibility* Drowsiness** Memory problems**
Other primary generalised (n=28)	Cognitive Function Questionnaire	Drowsiness*
Partial (n=21)	Conners Parents' Questionnaire	Impulsivity/hyperactivity* Psychosomatic**
	Cognitive Function Questionnaire	Distractibility* Drowsiness** Fear of failure* Memory problems*

$^{*}p<0·05$, $^{**}p<0·01$

(b) Changes during treatment

Table 10 shows the relatively few significant differences in behaviour scores between each treatment group and control children during the course of treatment. No consistent, meaningful pattern is seen up to the six month assessment (with the anomalous result that at three and six months into treatment the children with epilepsy treated with carbamazepine had lower inattention scores than controls), and at 12 months of treatment no differences at all were found.

Discussion

This study was essentially concerned with sodium valproate and carbamazepine as typically used in general paediatric practice. The main findings were that these drugs were equally effective in producing seizure control without common serious adverse physical complications, and that they were also equivalent in being associated with no reduction in intelligence and school attainments over the first 12 months of treatment. Children taking either type of medication showed inferior scores on various tests of specific cognitive ability, mainly those involving aspects of attention, over the 12 month period. In contrast, no behavioural differences between treated children with epilepsy and their controls were found after 12 months of treatment and at earlier stages of treatment only a few inconsistent differences of uncertain significance. It is possible that, in any case, these differences between the children with epilepsy and their controls were not drug effects at all but the result of remaining overt seizures or subtle seizure discharge both of which are capable of producing psychological effects.[7]

A main concern in the design of the study was to study schoolchildren with epilepsy in the community under the care of the local paediatric services—that is representative of children with epilepsy in general rather than those attending special clinics or services because of the severity of their disorder. The types of epilepsy exhibited by the children studied and the high rate of response to antiepileptic treatment both indicate the representative nature of the sample

Table 10 Difference in behaviour scores between each treatment group and controls on each assessment after introduction of treatment

Time of assessment after introduction of treatment (months)	*Treatment group (worse than controls unless otherwise indicated)*	*Questionnaire*	*Factor*
1	Sodium valproate	Cognitive Function Questionnaire	Social isolation*
3	Sodium valproate	Cognitive Function Questionnaire	Distractibility* Fear of failure*
	Carbamazepine	Conners Teacher Questionnaire	Inattention* (better than controls)
6	Carbamazepine	Conners' Teacher Questionnaire	Inattention* (better than controls)
12	No significant differences		

$^{*}p<0·05$, $^{**}p<0·01$

obtained. A basic principle was to avoid interfering with paediatricians' usual practice for the purpose of the study. Ethics approval was based on that understanding. In particular, random assignment of the children to treatment with either sodium valproate or carbamazepine was not considered justifiable. This would have especially been so in the case of absence epilepsy (13 of the 63 children with epilepsy) for which carbamazepine is acknowledged to be ineffective and sometimes harmful. The difficulties in obtaining matched controls for all the children with epilepsy were unsurmountable in the circumstances. However, inclusion of a comparison group of normal children was essential to control for developmental changes and other possible explanations of improvements over the course of the study.

The psychological measures used in this study were carefully selected and the repeat reliabilities of the specific ability tests specially assessed before the study to ensure that the tests were satisfactory in this respect. The repeated assessment procedures, and the test battery, proved acceptable to children, parents and teachers; no child was withdrawn during the study. The psychological assessments before the start of treatment were of particular importance in providing baselines with which later assessments could be compared, but also in identifying pretreatment differences in intelligence and attainment between boys and girls, and the behavioural differences between the normal control children and those with epilepsy before their treatment was started. These differences indicated the need for statistical adjustment to make later comparisons valid.

These pretreatment differences between the children with epilepsy and their controls are of considerable interest in themselves, especially in view of the differences in this respect between the main overall types of epilepsy. The partial seizures subgroup displayed the greatest variety of differences regarding specific abilities, whereas most behavioural differences were seen in the children with absence seizures followed by the partial seizures subgroup. There is no clear separation between these subgroups regarding particular types of differences from controls. Perhaps the most consistent element throughout these differences in the results of specific ability testing and behavioural ratings by both parents and teachers is inattentiveness of one sort or another. The differences in this respect (obviously not attributable to treatment in this instance) are in keeping with the general tendency for children with epilepsy to be considered 'inattentive',[8] including being perceived by their teachers as having poor concentration and mental processing and being less alert than their non-epileptic peers even when matched for overall school attainment level.[6] In the last mentioned study, children with a past history of epilepsy but no longer taking antiepileptic drugs because of apparent remission of their seizures, were still considered by their teachers to be less alert than their non-epileptic counterparts. The possibility exists that some children with epilepsy, irrespective of type, have a form of attentional disorder, related to impaired alertness, to which untreated seizures and some form of treatment can make a contribution, but which is not wholly explicable in these terms. The idea of an attentional deficit persisting in between seizures is not new. Mirsky and van Buren suggested this some time ago, at least in the case of absence seizures.[9]

It is interesting that the reassuring results for both drugs used in the present study are generally mirrored in studies of adult patients taking either sodium valproate or carbamazepine singly (for example see Gillham *et al*[10]). However, because of the complexities of trying to compare findings on patient groups of widely different ages, types of epilepsy, and other possible determinants of behavioural outcome, the present discussion is confined to other studies of children.

Comparisons between the findings in the present study and other reports concerning children is itself difficult enough in view of differences in study design. The nearest comparison is that with the study by Forsythe *et al* in which 64 children with newly diagnosed tonic-clonic or partial seizures (age 5 to 14 years) were randomly assigned to treatment with carbamazepine, phenytoin, or sodium valproate.[11] The children were assessed prospectively over a 12 month period on a range of cognitive function tests that were mainly concerned with visual or auditory memory but that also included tests of vigilance, concentration, and speed of information processing. None of these measures were the same as those used in the present study apart from additional measures of intelligence and reading (but only taken after the start of treatment) and no standardised assessments of behaviour were employed. Assessments were performed before treatment and at intervals of one, six, and 12 months after the start of treatment. A fifth of the original sample were lost to the study but in the remainder seizures were controlled in every case. A control group contained 31 children with nocturnal enuresis and nine with migraine. Analysis of the findings was limited for a variety of reasons and the main effect reported was an association between carbamazepine treatment (at modest dosage) and impairment at six and 12 months on a composite measure of memory function. As no pretreatment measures of intelligence and school attainments were made, the relevance of this memory deficit to more global measures, including educational attainment, remains unclear.

The results of other studies of children taking sodium valproate or carbamazepine as single treatments are generally difficult to interpret. Herranz *et al* reported various adverse behavioural effects in 64% of children after the introduction of sodium valproate, but the assessments used in this study were not psychometrically evaluated and did not include pretreatment measures.[12] In addition the children studied were mixed regarding severity of seizure disorder and intelligence and the body weight related dosage varied widely. Silverstein *et al*, in another uncontrolled study, reported a wide range of adverse behavioural effects after treatment with carbamazepine but some of the same criticisms apply to this report and its lack of detail makes evaluation difficult.[13] Schain *et al* demonstrated attentional and perceptual improvements at four to six months of carbamazepine treatment compared with previous treatment with sedative type antiepileptic drugs[14]; clearly, the design and permissable conclusions from this study are very different from those of the present investigation. In the study by Jacobides improvements in arithmetic were reported over a year in 22% of children after treatment with carbamazepine and in 35% maladjustment ratings were said to fall.[15] Other improvements reported in this account were increases in IQ and greater alertness. Unfortunately, evaluation of these claims is hampered by lack of detail and the absence of controls. Part of a complex study reported by Trimble and Cull consisted of the comparison of small groups of children with epilepsy taking either sodium valproate or carbamazepine.[6] Significantly better reaction times and scores on various cognitive tests were reported in children taking carbamazepine compared with those on sodium valproate. The report by Aman *et al* that cognitive function measures were best shortly after taking carbamazepine (near peak concentration) raises unanswered questions about the factors mediating such drug effects.[17]

These reports concerning children provide additional evidence of the inconsistent results of studies of the psychological effects of antiepileptic drugs, and the difficulties of interpreting the findings in view of various methodological designs and shortcomings, especially failures to control for relevant factors. No two studies are even remotely alike in the composition of the groups studied, the measures used, the attempt to control for developmental variables or the various factors, in addition to antiepileptic drug treatment, that influences cognitive or behavioural outcome. There is clearly a need to standardise assessment and procedures in future studies.

In the meantime, it seems safe to conclude that the weight of evidence is in favour of sodium valproate and carbamazepine deserving their reputation that, as typically used in paediatric practice, they are effective treatments that generally do not have adverse consequences of practical clinical significance.

We are most grateful to the children and parents who took part in this study and to the many paediatric colleagues who very kindly referred cases to us and also helped us with arrangements. We also thank Sanofi Labaz and Ciba Geigy for the financial assistance with the investigation and especially Dr Derrick Easter for his unfailing help and advice

Appendix: descriptions of specific ability tests

CANCELLING TEST[18]

Measures ability to establish an attentional set and the rate at which this is established. There are five timed trials where the child cancels the letters among digits and a reverse category trial requiring cancellation of digits from among letters. This reverse category trial shows any difficulty in switching attentional set. Test-retest reliability 0·89.

FOCAL ATTENTION TEST[19]

This provides a measure of the ability to focus attention on relevant items in the presence of distracters. The target is always an orange circle which is initially set among different colour circles and later among circles and squares. The number of distracters is increased over three trials. The child sorts the cards into those showing the targets and those without. Test-retest reliability 0·6.

SUSTAINED ATTENTION TEST[20]

A measure of the ability to sustain attention during a monotonous task lasting just under 15 minutes. The child is asked to identify animal names among other words presented at a standard rate of one every 2 seconds. Test-retest reliability 0·73.

MEMORY FOR STORIES[21]

A measure of memory for meaningful material that exceeds the short term span. The stories have short episodes and little redundancy but the material must be interpreted and structured to be remembered well. Two stories are given at the start of the session for immediate recall. At the end of the session the children are assessed for delayed recall and comprehension questions are asked. Test-retest reliability 0·6.

PEGBOARD[22]

A measure of visuomotor coordination and fine hand control. Children are asked to insert a row of pegs using first the dominant hand and then the nondominant hand. Lastly a row of alternate colours is made using alternate hands. Test-retest reliability 0·6.

DIGIT SYMBOL SUBSTITUTION TEST

This is a subtest from the WISC-R. It is a complex task involving attention, visual search memory and visuomotor coordination.

The above references describe versions of the tests which were either used or modified for use in the present study. All test-retest reliabilities were statistically significant.

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Sisters of fragile X boys

Inheriting the fragile X gene and showing the fragile X abnormality on cytogenetic analysis, it seems, are not the same thing. It is estimated that, of those who inherit the gene, about 80% of males and 50 to 60% of females show the chromosomal abnormality and develop the clinical syndrome. A recent study from Denver, Colorado (Randi J Hagerman and colleagues, *Pediatrics* 1992;**89**: 395–400) details the findings in the sisters of boys with the fragile X syndrome.

Thirty two fragile X girls were examined of whom 26 were sisters of an affected boy, three were cousins of such a boy, and three had presented because of their own problems and had no affected male relative. All were examined by the same person who was unaware of the cytogenetic findings. Eighteen chromosomally normal sisters of fragile X boys acted as the control group. The two groups of girls were assessed as regards physical features, intelligence, and behaviour.

On clinical examination six features were significantly more common in fragile X girls. They were prominent ears, a long face, shyness, poor eye contact, hand flapping, and hand biting. The control group had a mean IQ of 109 compared to 80 in the fragile X girls of whom 53% had an IQ of less than 85 and 25% less than 70. Fragile X girls with a normal overall IQ often had learning difficulty especially in mathematics. Ten in the fragile X group but none in the control group satisfied criteria for the diagnosis of attention deficit hyperactivity disorder. They were usually impulsive and distractible with a short attention span rather than hyperactive. The authors report that many of the girls improved on treatment with either stimulant drugs or folic acid but they present no controlled data.

This study demonstrates the differences between the fragile X sisters of fragile X boys and their chromosomally normal sisters but it was not a population study and may not, therefore, give a complete picture of the possible range of findings in fragile X girls.

ARCHIVIST

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Diagnostic significance of ^{99m}Tc-dimercaptosuccinic acid (DMSA) scintigraphy in urinary tract infection

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Abstract

A total of 106 children with symptomatic urinary tract infection (73 girls and 33 boys, 0–15·9 years of age) were studied by means of a dimercaptosuccinic acid (DMSA) scan, renal ultrasound, and a desmopressin test during infection and at follow up approximately two months later. At follow up they were also investigated by means of intravenous urography (IVU) and micturition cystourethrography (MCU).

During infection 23 children had a normal DMSA scan while 83 children had an abnormal one. The median C reactive protein and SD score for renal concentration capacity in the former group were 15 (range <10–178) mg/l and −1·0 SD score (range −2·4 to 1·8), respectively, and in the latter group 98 (range <10–320) mg/l and −3·1 SD score (range −5·7 to 1·1), respectively. In the former group there was no significant finding in any child on ultrasound or IVU and only one had significant vesicoureteric reflux (VUR) (grade 3).

At follow up 51 children had a normal DMSA scan while 55 children showed persistent changes. The median SD score for renal concentration capacity in the former group was −0·9 SD score (range −3·2 to 1·4) and in the latter group −1·6 SD score (range −4·6 to 2·5). No significant changes were found in the former group on ultrasound or IVU and only two children had significant VUR (grade 3). In the latter group 20 children showed changes on ultrasound, 15 showed changes on IVU, and 23 had VUR.

These results suggest that a normal DMSA scan during or approximately two months after urinary tract infection in children indicates a low risk of finding significant pathology of the urinary tract.

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The cumulative risk of contracting a symptomatic urinary tract infection during childhood is 3% for girls and 1% for boys.[1] If not treated and controlled properly a urinary tract infection may have serious long term consequences.[2] The protocol for the investigation and follow up of children with urinary tract infection has recently been the subject of debate.[3, 4] Most authors, however, recommend some combination of renal ultrasound, intravenous urography (IVU), a dimercaptosuccinic acid (DMSA) scan, and micturition cystourethrography (MCU).[5–7] Children with urinary tract infection therefore require great resources in the health care system. At times when economic resources are limited, ways to simplify and rationalise the investigations and follow up of these children without sacrificing safety would be of value. Moreover, diagnosis of urinary tract infection in small children is not always easy with the available indirect parameters. A more direct approach to the diagnosis in these cases could be helpful in identifying children at risk. It has been shown previously that a DMSA scan is a sensitive method to diagnose and localise acute pyelonephritis in children[8] and to detect renal scars.[9, 10] This raises the question of to what extent the DMSA scan can replace other radiological methods as a routine investigation in children with urinary tract infection. The significance of a normal or an abnormal DMSA scan during or shortly after infection is not well documented, however. The purpose of this study was to find out if a DMSA scan was more sensitive to distinguish between upper and lower urinary tract infection than other commonly used parameters and to evaluate the predictive value of a normal DMSA scan in children with urinary tract infection.

Patients and methods

A total of 106 children admitted to the hospital with symptomatic urinary tract infection (33 boys and 73 girls, 0–15·9 (median 0·7) years of age) were included in the study after obtaining informed consent from the parents. The age and sex distribution of the children is shown in fig 1. The primary symptoms were fever, failure to thrive, or feeding difficulties. The children were investigated according to the following protocol. On admission a blood sample was taken for the determination of C reactive protein. Ultrasound, a DMSA scan, and a desmopressin test were performed within five

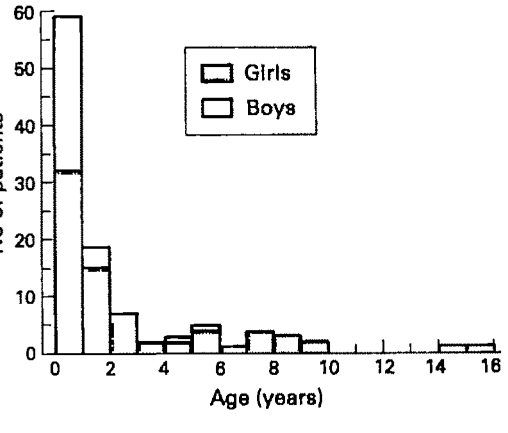

Figure 1 Children grouped by age and sex.

days after admission. After 6–20 (median 8) weeks these investigations were repeated and IVU and MCU were also performed. All children were treated with antibotics for at least 10 days and after this prophylactic low dose antibiotic treatment was administered until the follow up investigation. No child had a breakthrough infection during the interval between the first and second investigations.

DMSA SCAN

The children were examined supine and immobilised in a vacuum pillow. ^{99m}Tc-DMSA was given in a dose of 0·5 MBq/kg body weight (minimum 10 MBq). At least three hours after injection one anterior and one posterior picture with a 10 minute acquisition time (n=24) or a 500 000 count posterior picture (n=82) was taken. All DMSA scans were evaluated visually and each kidney was subjectively judged to be normal or abnormal.

ULTRASOUND

Ultrasound was performed with 3·5 or 5 MHz sector scanners. Changes on ultrasound were considered present if changes in parenchymal echogenicity and/or dilatation of the pelvis were observed.

IVU

IVU was performed according to standard procedures and changes were considered present if renal scarring, hydronephorosis, ureteric dilatation, or malformations were observed. Renal scarring was defined as a combination of parenchymal reduction and deformities of calices.[11]

MCU

The presence of reflux was noted at MCU and graded on a scale from 0 to 5 in accordance with the International Reflux Study.[12]

DESMOPRESSIN TEST

Desmopressin (Minirin, Ferring) was administered intranasally, 10 µg for infants and 20 µg for children over 1 year of age. One hour later three consecutive urine samples were collected and the highest urine osmolality was taken as a measure of the maximum urinary concentration ability. A SD score was calculated according to Mårild *et al.*[13]

STATISTICS

Mann-Whitney's non-parametric test was used for statistical analyses, a p value <0·05 being considered significant.

This study was approved by the local ethics committee.

Results

During infection 23 children (13 boys and 10 girls, 0–3·6 (median 0·2) years of age) had a normal DMSA scan. Eighty three children (20 boys and 63 girls, 0·1–15·9 (median 1·0) years of age) had an abnormal DMSA scan (130 kidneys). The age distribution of children below 1 year of age in relation to findings on DMSA scan during infection is shown in fig 2. At follow up no child in the normal group showed changes in the DMSA scan and 28 children originally with an abnormal DMSA scan had become normal. Thus at follow up 51 children had a normal DMSA scan and 55 children had persistent changes in 68 kidneys.

LABORATORY PARAMETERS

The C reactive protein concentration during infection in the two groups is shown in fig. 3. The median C reactive protein in the patients with normal DMSA scan was 15 mg/l, significantly lower than in those with abnormal scans where the median was 98 mg/l (p<0·001). In the normal group, 10 out of 23 children had a C reactive protein concentration >20 mg/l, which might indicate that they had acute pyelonephritis. In seven of these children, all with C reactive protein >32 mg/l, there was, however, an ongoing upper respiratory tract infection that might have been responsible for the raised C reactive protein. In the abnormal group, six children had a C reactive protein concentration <20 mg/l, indicating a lower urinary tract infection. Therefore, the C reactive protein did

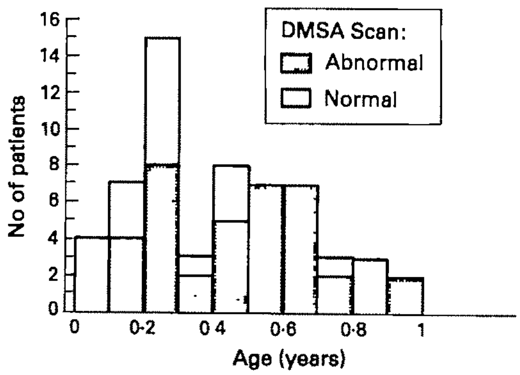

Figure 2 Distribution of findings on DMSA scan in children below 1 year of age.

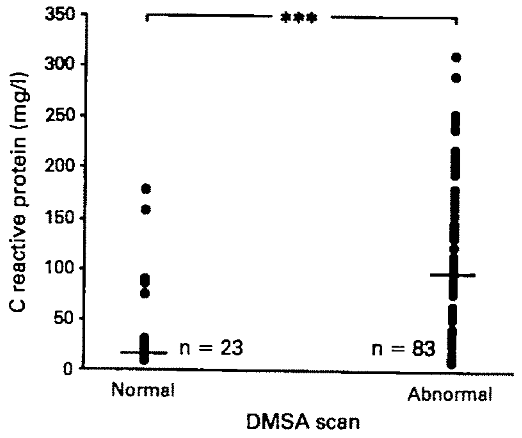

*Figure 3 C reactive protein concentration in children with a symptomatic urinary tract infection and a normal or abnormal DMSA scan. The lines indicate the median values. ***=p<0·001.*

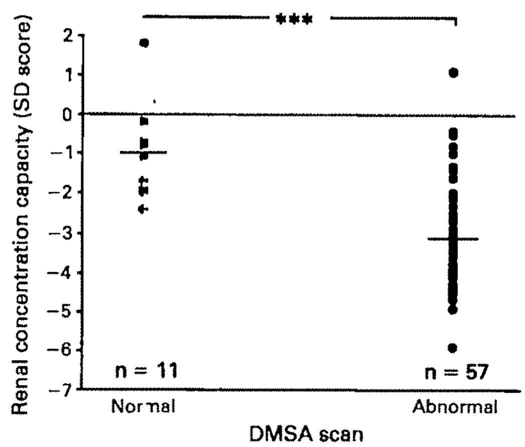

*Figure 4 The SD score for renal concentration capacity according to Mårild et al[13] in children with a symptomatic urinary tract infection and a normal or an abnormal DMSA scan. The lines indicate the median values. *** =p<0·001.*

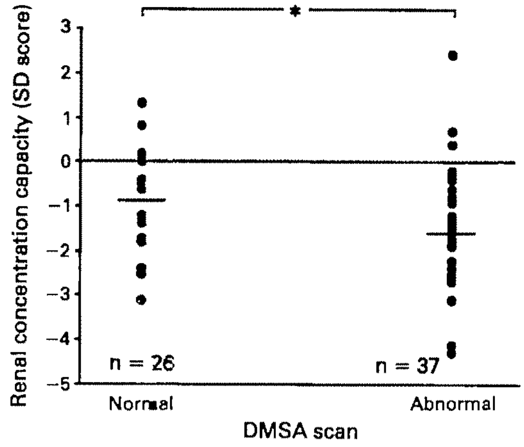

*Figure 5 The SD score for renal concentration capacity according to Mårild et al[13] approximately two months after a symptomatic urinary tract infection in children with a normal or an abnormal DMSA scan performed at the same time. The lines indicate the median values. * =p<0·05*

Table 1 Children investigated with a DMSA scan during infection who showed changes in ultrasound during infection and IVU and MCU at follow up. Figures are number of children (kidneys)

During infection		*Abnormal at follow up*	
DMSA scan	*Abnormal on ultrasound*	*IVU*	*MCU*
Normal 23	5 (6)	2 (3)	3 (6)
Abnormal 83 (130)	20 (22)	15 (20)	23 (34)

Table 2 Changes found on ultrasound, IVU, and MCU in children with a urinary tract infection and investigated with a DMSA scan during infection and at follow up after approximately two months Figures are number of children (kidneys)

	During infection		*At follow up*	
	Normal	*Abnormal*	*Normal*	*Abnormal*
Findings on ultrasound				
Changes in echogenicity		10 (11)		1 (1)
Hydronephrosis		2 (2)		1 (1)
Slight dilatation	5 (6)	8 (9)	3 (4)	2 (2)
Findings on IVU:				
Renal scarring		5 (8)		5 (8)
Hydronephrosis		2 (2)	1 (1)	1 (1)
Double ureters		6 (8)	1 (1)	5 (7)
Slight dilatation	2 (3)	2 (2)	2 (3)	2 (2)
Findings on MCU				
VUR grade ≥3	1 (2)	14 (19)	2 (3)	13 (18)
VUR grade <3	2 (4)	9 (15)	3 (5)	8 (14)

not agree with findings on the DMSA scan in 16 children (15%).

During infection the SD score for renal concentration capacity was available for 68 children and is shown in both groups in fig 4. The median SD score for the abnormal group was significantly lower than in the normal one ($p<0\cdot001$), but there was overlapping between the two groups. In the normal group, one child had an SD score <-2 SD score, while in the abnormal group, 10 children had a normal SD score (>-2 SDS). Thus in 16% of the children there was a disagreement between findings in the DMSA scan and the desmopressin test. At follow up, the SD score for renal concentration capacity was available for 63 children. It was significantly lower in the children with DMSA changes than in those without ($p<0\cdot05$) (fig 5), but there was a large overlap between the two groups.

RADIOLOGICAL FINDINGS

DMSA scan during infection

The number of children investigated with a DMSA scan during infection and with abnormal findings on ultrasound at the same time is shown in table 1. The findings are specified in table 2. Five children with a normal DMSA scan showed changes on ultrasound, but these changes were only a slight dilatation of the renal pelvis without clinical significance (table 2). Altogether 24% of children (17% of kidneys) with changes in the DMSA scan during infection showed abnormal changes on ultrasound (table 1). In the normal group no child was found to have significant changes at IVU (tables 1 and 2). All children with renal scarring on IVU showed severe changes in the DMSA scan (table 2). Among the children with a normal DMSA scan during infection, only one child was found to have a significant verisicoureteric reflux (VUR) (bilateral grade 3). This was a 5 month old boy who had a prominent renal pelvis on ultrasound during infection.

DMSA scan at follow up

The number of children in each group with findings on ultrasound, IVU, and MCU is shown in table 3 and the findings are specified in table 2. In the normal group no child had significant changes on ultrasound or IVU. The one child with hydronephrosis on IVU and a normal DMSA scan at follow up did not have a significant obstruction and required no intervention. All kidneys with established scars at IVU showed changes in the DMSA scan. The overall frequency of VUR was 25%. Five children with a normal DMSA scan at follow up

Table 3 Children investigated with a DMSA scan at follow up who showed changes in ultrasound, IVU, and MCU at follow up Figures are number of children (kidneys)

DMSA scan at follow up	*Abnormal at follow up*		
	Ultrasound	*IVU*	*MCU*
Normal 51	3 (4)	4 (5)	5 (8)
Abnormal 55 (68)	4 (4)	13 (18)	21 (32)

had VUR, but it was significant in only two children (grade 3 reflux in three kidneys).

Discussion

It is important to bear in mind that all children in the present study were hospitalised and investigated because of a symptomatic urinary tract infection. The primary symptoms were therefore those commonly associated with an upper urinary tract infection: fever, feeding difficulties, and failure to thrive. The median age of the children with a normal DMSA scan during infection was very low (fig 2). The normal DMSA scan in this group could therefore have two explanations. Either the DMSA scan may not be a sufficiently sensitive method to diagnose acute pyelonephritis in infants or these infants had in fact a lower urinary tract infection. However, seven of the 10 children in this group with clinical and laboratory parameters suggesting the presence of acute pyelonephritis had an ongoing upper respiratory tract infection. We believe that these children actually had a primary upper respiratory tract infection with concomitant bacteriuria. ^{99m}Tc-DMSA is taken up by the proximal tubular cells by an active process.[14 15] The normal DMSA scans seen in the smallest infants suggest that this process already is mature in these infants, although this may vary between individual infants. In our experience, however, the quality of the DMSA scan in infants under 2–3 months of age is not always satisfactory and it would seem wise not to rely on this method to diagnose acute pyelonephritis in these young infants.

The renal concentration capacity is often used to differentiate an upper urinary tract infection from a lower one.[16] In the present study the renal concentration capacity was significantly lower in the children with changes in the DMSA scan both during infection and at follow up. However, there was a marked overlapping between the two groups at all times, making it difficult to predict changes in the DMSA scan from the desmopressin test. Moreover, for children under 6 months of age, normal values for the concentration capacity are not available.[17] Therefore, although the desmopressin test shows a difference between the two populations with a normal and an abnormal DMSA scan, it is not a reliable test to differentiate an upper urinary tract infection from a lower one in individual cases. A non-invasive direct method for diagnosing an upper urinary tract infection in children is needed. The use of ultrasonography in this respect has not turned out to be as successful as was initially hoped, as shown by the present study and others.[8 18] In the majority of cases the differentiation between lower and upper urinary tract infection can be made on a clinical basis, however. We therefore believe that in children over 3 months of age in whom acute pyelonephritis is suspected but clinical and laboratory parameters are ambiguous, a DMSA scan should be performed in order to verify the diagnosis. This procedure could help to identify the children who are at risk and spare many children unnecessary investigations and follow ups.

Abnormal findings in other radiological investigations were scanty in children with a normal DMSA scan. The most common finding on ultrasound or IVU in these children was a slight dilatation of the renal pelvis or ureter that was considered to be of no significance. In these cases the presence of VUR was suggested and this was the case in five out of six kidneys. The presence of double ureters was easily detected by IVU but was not detected by the DMSA scan. Although this finding is usually considered to be of no significance, it is interesting to note that all these kidneys showed defects in the DMSA scan during infection and all but one at follow up. This suggests that these kidneys are at risk in children with a urinary tract infection and is in agreement with a previous report.[19]

The overall frequency of VUR in the present study was 25%, which is similar to that reported by others.[5 20 21] During infection VUR was associated with DMSA changes in all but three children and in only one child was the reflux significant (grade 3). This child showed a slight dilatation of the renal pelvis on ultrasound. At follow up the DMSA scan had become normal in an additional two children with VUR, one of whom had a significant reflux (grade 3). The children with significant reflux were boys aged 3 and 5 months. MCU is the definitive method of demonstrating VUR, although radionuclides are being used more frequently.[22] MCU is a rather unphysiological investigation and is often a cause of great distress in children and parents. Most authors agree that an MCU should be carried out in all children with urinary tract infection under the age of 1 year as these children are at high risk of developing renal damage.[23 24] Whether this investigation should be performed routinely in older children with a urinary tract infection is a matter of debate.[3 4 25] In the present study, a normal DMSA scan indicated a low risk of finding a significant pathology of the urinary tract. It would therefore seem safe not to perform MCU as a routine investigation in children with a urinary tract infection over 1 year of age, provided that they have a normal DMSA scan either during or approximately two months after infection and a normal ultrasound during infection.

In conclusion, our present results indicate that a DMSA scan is a sensitive method to distinguish between upper and lower urinary tract infection in children and we suggest that it should be used to verify the diagnosis in children in whom there is a suspicion of acute pyelonephritis but the clinical and laboratory parameters are ambiguous. Moreover, the results indicate that an MCU may be safely omitted as a routine investigation in children over 1 year of age with a urinary tract infection who have a normal DMSA scan during infection or at follow up approximately two months after infection and a normal ultrasound during infection.

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Foregut motor function in chronic renal failure

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Abstract

In children with chronic renal failure (CRF) anorexia, nausea, and vomiting are common yet poorly understood symptoms. We studied oesophageal and gastric motor function in 12 children (age 7 months–6·8 years) with severe CRF not undergoing dialysis who had persistent anorexia and vomiting. Eight of 12 patients had significant gastro-oesophageal reflux (reflux index 5·2% to 21·9%, mean 11·3%; controls <5%), 7/10 had altered gastric half emptying times (T½) for 5% glucose or milk (glucose meal—controls: 8–14 min, two CRF patients: 18–25 min; milk meal—controls: 48–72 min, five CRF patients 27, 28, 82, 83, and 110 min). Gastric antral electrical control activity was abnormal in 6/11 patients, with different types of gastric dysrhythmias whereas the remainder and controls showed a regular dominant frequency of 0·05 Hz. In 7/9 patients fasting serum gastrin concentration was raised (53 to >400, mean 168 pmol/l, controls <40 pmol/l). All CRF patients with anorexia and vomiting had one or more disorder of foregut motility. The nature and variety of the motor disorders and the raised concentrations of circulating gastrin suggest that the normal environment generated by CRF affects the function of the smooth muscle of the foregut.

(*Arch Dis Child* 1992;67:1343–7)

Children with chronic renal failure (CRF) commonly suffer from anorexia, nausea, vomiting, and failure to thrive.[1] Our current understanding of the cause of these symptoms is limited and treatment is largely empirical and ineffective. It is generally accepted that vomiting may occur as a result of gastro-oesophageal reflux (GOR) or by initiation of the emetic reflex. The latter is associated with prodromal symptoms such as nausea, gastric and oesophageal dysmotility and reflex contractions of the intercostal, diaphragmatic, and anterior abdominal muscles.[2] Regurgitation however is effortless and not associated with any prodromal symptoms.[3] Whether one or both of these mechanisms is responsible for vomiting in children with CRF has not been previously studied.

In this study we have assessed foregut motor function and its regulation in children with CRF who were failing to thrive and had symptoms of anorexia and vomiting.

Patients and methods

PATIENTS

Twelve children (10 boys and two girls, mean age 2·17 years, range 7 months–6·8 years) with CRF (mean estimated glomerular filtration rate 11 (range 6–25) ml/min/1·73 m^2) receiving conservative medical management but not requiring dialysis were studied. The primary cause of renal disease was renal dysplasia (n=7) or obstructive uropathy (n=5). At the time of study the mean height SD score was −2·6 (−4·0 to −1·7) and mean weight SD score was −2·5 (−3·8 to −1·3). All children were anorexic and/or had a history of vomiting at the time of study. Eleven of the 12 required nasogastric tube feeding in order to achieve an adequate energy intake.

CONTROLS

Overall 50 subjects (age 3 months–17 years) acted as controls: 22 for GOR, 12 for gastric emptying, and 16 for gastric electrical activity. Twelve were normal healthy children and the others had eating disorders (n=23), recurrent respiratory infections (n=6), cyclical vomiting (n=5), postenteritis enteropathy (n=2), Crohn's disease in relapse (n=2); none had irritable bowel syndrome or were referred for a suspected gastrointestinal motility disorder. After detailed motility investigation including intraoesophageal pH monitoring, antroduodenal manometry and electrogastrography, no evidence of such a disorder could be found.

METHODS

All patients with a history of vomiting had a barium meal and follow through examination. Foregut motor function was assessed by measuring intraoesophageal pH, gastric emptying, and gastric antral electrical activity. Regulation of gastrointestinal motility was assessed by measuring polypeptide hormones. The study was approved by the ethical committee of the Hospital for Sick Children, Great Ormond Street.

GOR

A well validated ambulatory intraoesophageal pH monitoring system (Synectics Medical) utilising an antimony electrode was used over a six hour postprandial period, which has been shown to be comparable with a 24 hour recording for the detection of GOR in children with vomiting and feeding problems.[4] Two parameters were considered: (1) percentage of time spent with an intraoesophageal pH below 4 (reflux index or RI) and (2) duration of the longest reflux episode. GOR was graded as normal (RI ≤5%), mild (RI 5%–10%), moderate (RI 10%–20%), and severe (RI >20%).

Gastric emptying

Gastric emptying was measured by applied potential tomography.[5] Either 20 ml/kg of cows' milk (+0·22 g sodium chloride/100 ml to increase electrical conductivity) or 5% glucose were given as test meal. At the end of the study an emptying curve was computed, maximum postprandial resistivity noted, and time to half emptying (T½) calculated. Six patients were tested after a milk meal, three after a glucose meal, and three with both meals on two different occasions.

Gastric antral electrical control activity

Electrical control activity was recorded by surface electrogastrography[6] over a one hour period after an overnight fast. A standardised meal (milk 10–20 ml/kg) was given after 30 minutes to initiate postprandial activity. Electrical activity was recorded from four pairs of silver/silver chloride bipolar skin electrodes (impedance 2·5+2·0 KOhms) placed over the abdomen halfway between the xiphisternum and the umbilicus. The signal was then amplified and low pass filtered at 0·33 Hz before being displayed on a Gould 8 channel polygraph and simultaneously digitalised at 1 Hz by an analogue to digital converter Data Translation DT 2801A mounted in an IBM AT compatible personal computer (Zenith 248). Running spectral analysis of the signal was performed using a sequence of computerised algorithms (PC-DATS, Prosig Computer Consultants) customised by the authors. Each one hour recording was divided into 55 partially overlapping segments of 128 seconds. Each segment was band pass filtered at 0·01 and 0·25 Hz and the frequency spectrum was derived by autoregressive modelling. The dominant frequency was calculated and the resulting analysis was displayed as a pseudo three dimensional plot.

Polypeptide hormones

Fasting blood samples were collected in 5 ml lithium heparin test tubes with 0·2 ml Trasylol. The samples were centrifuged, the serum removed, and they were immediately frozen in liquid nitrogen and then stored at −70°C. Serum concentrations of gastrin, glucagon, pancreatic polypeptide, vasoactive intestinal polypeptide, and neurotensin were measured using well validated radioimmunoassays (Professor S R Bloom, Supraregional Assay Service, Hammersmith Hospital, London).

STATISTICAL ANALYSIS

Given the small numbers of subjects tested and the variability of data distribution, arbitrary upper and lower limits of normal (greater than 2SD from the controls' mean) were established. Patients groups were compared with controls using the Mann-Whitney test.

Results

GOR

In 22 age matched controls mean (SD) RI was 2·22 (1·22)% compared with 8·02 (6·79)% in CRF patients (difference between medians −5·21, 95% confidence interval −7·86 to −1·18; p=0·01), and RIs are shown in fig 1. Eight patients with CRF had GOR (RI >5%)—five mild, two moderate and one severe—and in these mean RI was 11·3 (range 5·2–21·9)%. Three patients with GOR also had long reflux episodes (22, 27, and 30 min) exceeding the upper limit of controls (20 min). The severity of reflux was not directly related to the degree of the CRF.

Gastric emptying

Only two patients managed to drink the full test meal; in the remainder (n=10) it was given by nasogastric tube but six could only tolerate volumes of 10 to 15 ml/kg, that is 50% to 75% of the meal volume normally used. Four patients (three tube fed) vomited during the test. As expected, the T½ was considerably slower with milk than with 5% glucose in both patients and controls (fig 2). After the milk meal, the mean (SD) T½ was 61·5 (8·6) min in six healthy controls (normal limits: 40 and 80 min) and 62·8 (26·8) min in nine CRF patients. After the glucose meal, the mean (SD) T½ was 10·7 (2·3) min in six other healthy controls (normal limits: 6 and 16 min) and 13·2 (7·6) min in six CRF patients. Seven patients had abnormal gastric emptying. Two had accelerated gastric emptying, one after the milk meal and another after both milk and glucose meals (T½ 28, 27, and 5 min respectively). Five had delayed emptying, three after the milk meal (T½ 82, 83, and 110 min) and two after the glucose meal (T½ 18 and 25 min). Although as a group patients did not significantly differ from controls (milk meal: difference between medians −1.25, 95·2% confidence interval −24·0 to 24·0, p=0·95;

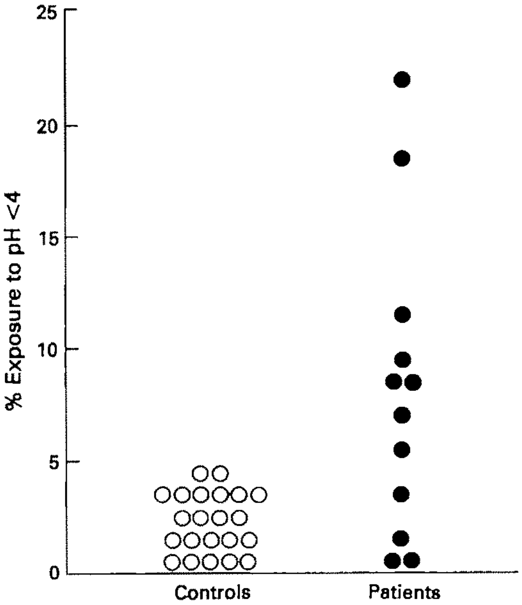

Figure 1 Percentage of exposure to intraoesophageal pH <4 (RI) in 22 controls and 12 patients with CRF.

glucose meal: difference between medians −1·0, 95·2% confidence interval −11·0 to 5·0; p=0·87), the variability of their T½ was clearly higher than that of controls. Of those patients with abnormal gastric emptying, half were intolerant of the test meal. Among the patients with delayed emptying, two vomited during the test and one received a reduced meal volume. One patient with accelerated emptying vomited at the end of the test.

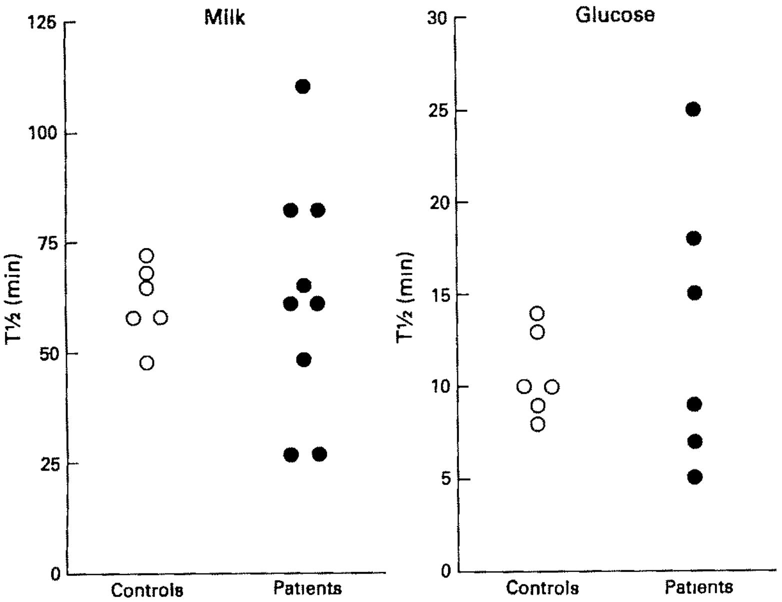

Figure 2 Gastric half emptying times (T½) after a milk meal and a 5% glucose meal in 12 healthy controls and 12 children with CRF. Note that the time scale on the Y axis of the right hand scatterplot is expanded.

Gastric antral electrical control activity

Electrical control activity occurred at a mean frequency of 0·05 (0·04–0·06) Hz in 16 controls and in five patients. In 6/11 children with CRF a number of different dysrhythmias of antral electrical control activity were detected. One patient had a tachyarrhythmia (0·15 Hz), two had a bradyarrhythmia (0·02 and 0·03 Hz respectively), and three had an unstable electrical control activity (no dominant frequency detectable). All dysrhythmias occurred during the fasting as well as the postprandial period. These dysrhythmias are shown as pseudo three dimensional running spectral frequency plots in fig 3.

Polypeptide hormones

Fasting serum concentrations of vasoactive intestinal polypeptide, pancreatic polypeptide, glucagon, and neurotensin were within the reference range in all but two patients, one with vasoactive intestinal polypeptide values of 48 pmol/l (reference range <30) and another with pancreatic polypeptide values of 393 pmol/l (reference range <300). Fasting serum gastrin was significantly raised in 7/9 patients. These seven had a mean value of 168 pmol/l and a range

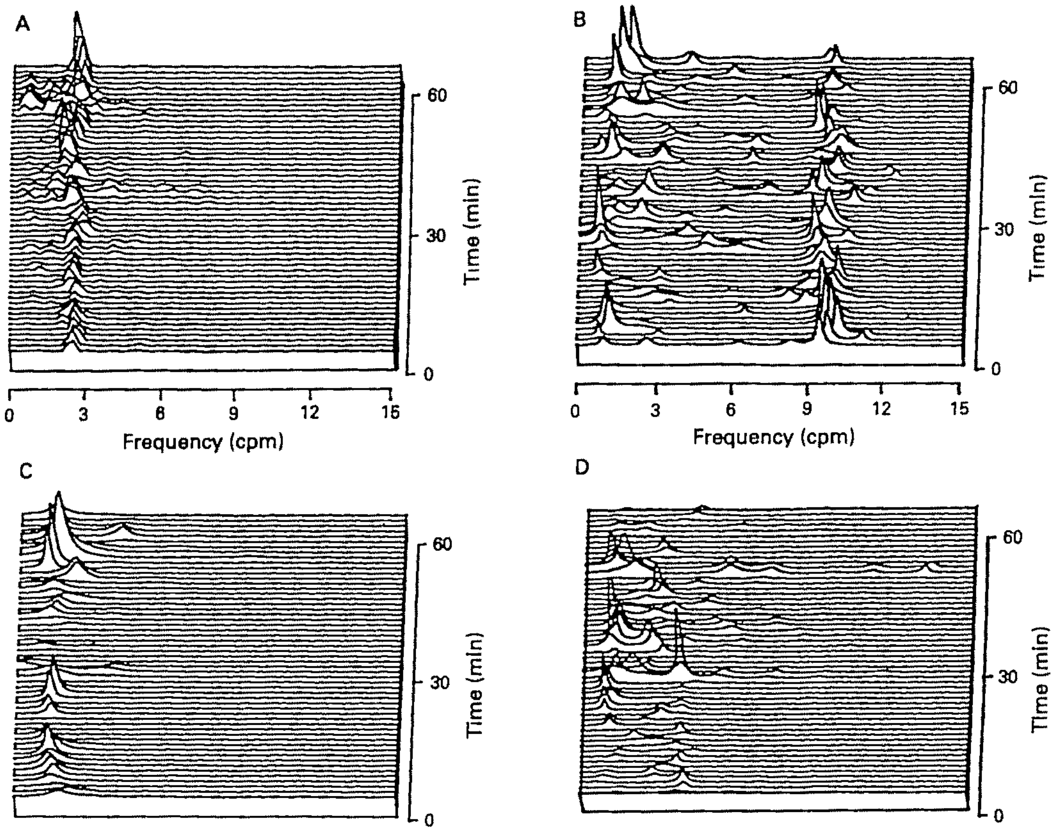

Figure 3 Pseudo three dimensional running spectral frequency plots of electrogastrography recorded in four children with chronic renal failure. Normal electrical control activity (A), a tachyarrhythmia (B), a bradyarrhythmia (C), and unstable electrical control activity (D) are shown Frequencies are expressed as cycles per minute (cpm), where 3 cpm=0·05 Hz.

Results of foregut motility assessment

Patient No	*GOR*	*Gastric emptying*	*Gastric antral electrical control activity*
1	Moderate	Delayed	—
2	Mild	Delayed	Normal
3	Normal	Normal	Tachyarrhythmia
4	Moderate	Accelerated	Unstable
5	Severe	Normal	Normal
6	Mild	Accelerated	Unstable
7	Mild	Normal	Bradyarrhythmia
8	Normal	Delayed	Normal
9	Normal	Normal	Bradyarrhythmia
10	Mild	Delayed	Normal
11	Mild	Normal	Unstable
12	Normal	Delayed	Normal

of 53–>400 pmol/l (reference range <40, remaining two patients 29 and 39 pmol/l). This finding was not related to any abnormality of blood chemistry or foregut motor function.

In summary—as can be seen from the table, all patients with CRF had some foregut motility disorder, either in the form of GOR (66·7%), abnormal gastric emptying (58·3%), or antral dysrhythmia (54·5%), and seven out of 12 (58·3%) had more than one abnormality, the most common association being between GOR and disordered gastric emptying.

Discussion

There is increasing evidence to suggest that anorexia, nausea, and vomiting result from a disturbance of foregut motility and its control mechanisms.[7] This study clearly demonstrates that there are widespread motilty disorders affecting the foregut of children with CRF who present with these symptoms. The prevalence of GOR was high (66·7%) and GOR was moderate to severe in 25%. These findings confirm the observations of Ruley *et al*, who found GOR in 16/22 (73%) infants with CRF and feeding problems.[8]

In this study, however, GOR was not the only cause of vomiting and abnormalities of gastric motor activity were as common. There have been no previous studies of gastric motor function in children with CRF, but studies in adults with CRF have yielded contradictory results. Some have shown delayed gastric emptying in symptomatic patients[9] and during continuous ambulatory peritoneal dialysis,[10] whereas normal gastric emptying has been reported in patients receiving haemodialysis, whether symptomatic or not.[11 12] Our findings of both delayed and accelerated gastric emptying might be surprising, but both are in keeping with the patients' symptoms of fullness, nausea, and vomiting.[13]

During the pre-ejection phase of the vomiting reflex gastric antral dysrhythmias commonly occur in association with nausea and other autonomic symptoms.[2] Gastric antral dysrhythmias have been described in different conditions in which the emetic reflex has been evoked[14–18] and in both adults and children with severe unexplained vomiting.[19–21] Although it might be expected that gastric electrical activity would affect gastric emptying, in only two patients was an antral dysrhythmia found as well as a disordered gastric emptying. The most likely explanation is that dysrhythmias result in impaired motor function of the gastric antrum which is mainly involved in grinding and emptying of solid foods. Emptying of a liquid meal depends mainly upon tonic pressure changes of the gastric fundus[22] and thus antral dysrhythmias may not affect emptying of a liquid meal such as 5% glucose or milk. Furthermore, some of the dysrhythmias that we detected were more subtle and less striking than the continuous 'tachygastria' observed by others in patients with intractable vomiting. They may have been sufficient to induce nausea (and thereby a reduced food intake) but insufficient to affect gastric emptying. Secondly, some patients did not have the same meal volume (as they did not all tolerate the full meal) or the same test meal during the applied potential tomography and electrogastrography studies and a different challenge on the stomach might have resulted in different functional consequences. Finally, in nearly all patients gastric electrical control activity and gastric emptying were studied on two different occasions. Thus day to day variations might have been responsible for the lack of correlation between gastric emptying and gastric electrical control activity, perhaps due to fluctuations of some polypeptide hormones metabolised by the kidney and active on gut motility and food intake.

Gastrointestinal motility is modulated by myogenic, neural, and humoral factors,[23] which may themselves be altered when the renal function is deranged. The variability of antral electrical control activity found in this study is in sharp contrast to the persistent dysrhythmias we have recently described in patients with disease of enteric nerves or smooth muscle.[24] Thus it is likely that our present findings result from an altered humoral environment. In adults with CRF abnormally raised serum concentrations of several polypeptide hormones have been reported and hypergastrinaemia is a prominent biochemical feature.[25 26] In response to a meal, gastrin increases and stimulates gastric acid secretion and gastrointestinal motor activity by increasing antral contractions and disrupting the fasting motility pattern.[27] At pharmacological doses, like those seen in CRF, gastrin stimulates oesophageal, gall bladder and small bowel contractions, as well as gastric acid and pancreatic exocrine secretion. Acid hypersection and disruption of the fasting motility pattern with increased but incoordinate small bowel contractions all result in delayed gastric emptying.[22] Therefore gastrin could be partly responsible for some of the motility disorders found in our study. However, other polypeptide hormones involved in the regulation of gut motility and the modulation of hunger and satiety are markedly increased in adults with CRF.[25] It is therefore very likely that in children with CRF hypergastrinaemia is only part of a more complex biochemical disorder that may be expected to have considerable effects on gut motility and food intake. In summary, this study demonstrates that children with CRF who suffer form anorexia, nausea, and vomiting have several motility disorders of the upper gastrointestinal tract. GOR is the cause of much vomiting, but reflex vomiting, with gastric dysrhythmias and disordered gastric emptying, is at least as common. We speculate that the altered humoral environment indicated by the hypergastrinaemia and generated by the CRF is at least in part responsible for the foregut motility disorders and the persistent anorexia.

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Ultrasonographic assessment of the extent of hepatic steatosis in severe malnutrition

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Abstract

Ultrasonographic, blinded assessment was made of the extent of hepatic steatosis in 55 children with severe malnutrition: undernutrition (n=6), marasmus (n=18), marasmic-kwashiorkor (n=17), and kwashiorkor (n=14). The children were examined on admission, in early recovery (considered as baseline), and again at discharge. Eleven healthy control children and eight of the previously malnourished children were studied as comparison groups.

Both oedematous and non-oedematous malnourished children had significantly more steatosis than the comparison groups at each time. Children with oedematous malnutrition had significantly greater steatosis than non-oedematous children at admission. Half of the non-oedematous malnourished children had appreciable hepatic steatosis at both admission and at baseline.

Hepatic fat was only slowly mobilised. The rate constant was 1·4±0·3%/day. One quarter of the children did not change steatosis grades during the period they were in hospital. There was no overall correlation between the extent of steatosis and liver size.

Hepatic steatosis in childhood malnutrition is not confined to oedematous children: it is frequently present in marasmic and undernourished children. Its extent is not necessarily related to the degree of hepatomegaly and accumulated lipid is only slowly mobilised.

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Kwashiorkor, or oedematous childhood malnutrition, was described by Cecily Williams in 1935. Her description included the statement: 'Post-mortem, the only constant finding is an extreme fatty infiltration of the liver'.[1] The precise pathogenesis of this accumulation of fat in the liver remains unexplained; however, the severity of the pathological change is beyond doubt. The median fat content of liver biopsy samples taken from severely malnourished Jamaican children was 30–35%, and it approached 50% of liver wet weight in the severest cases.[2] Whatever the pathogenesis, disturbances of liver function, such as increases in bilirubin[3] and serum transaminases,[4] carry a very bad prognosis.

Hepatic steatosis is usually held to be a clinical feature only of oedematous malnutrition[5] and standard textbooks categorically state that 'fatty liver does not occur in marasmus'.[6] Waterlow, however, mentions one marasmic child with a fat content of 35% liver wet weight,[2] and other authors have reported similar cases.[7–9] It is unclear if these are isolated cases or whether hepatic steatosis frequently occurs in marasmus and undernutrition—the non-oedematous forms of childhood malnutrition.

Previous studies have used chemical analysis or histological grading of liver biopsy tissue to assess liver steatosis. These series were, of necessity, limited to patients with definite indications for biopsy and therefore excluded both children with very severe illness and those with mild forms of the disease; further, in very few patients has more than a single assessment been made.

Recently ultrasonography has been validated and used to assess liver fatty infiltration in adults; the hepatic steatosis can be demonstrated with high sensitivity (94%) and specificity (84%).[10]

The aim of the present study was to examine the extent of hepatic steatosis, longitudinally, in an unselected series of severely malnourished Jamaican children.

Subjects and methods

STUDY CHILDREN

The study group comprised 55 children, 6 to 36 months old. They were consecutively admitted to the Tropical Metabolism Research Unit in Kingston, Jamaica, as a result of severe, primary malnutrition. A summary of their clinical details and diagnoses, using the Wellcome classification,[11] is given in table 1. The children were treated by standard protocols.[12] Their diet was based on an infant formula (Pelargon, Nestlé)

Table 1 The clinical details of the study children; values are mean (SD)

	Undernutrition (n=6)	*Marasmus (n=18)*	*Marasmic-kwashiorkor (n=17)*	*Kwashiorkor (n=14)*
Male female	5 1	13·5	11.6	9:5
Age (months)	18·6 (4·7)	16·7 (6·8)	12·3 (6·3)	12·8 (3·1)
Admission height for age (Z)	−2·7 (1·3)	−4·2 (1·6)	−4·2 (1·2)	−2·1 (1·0)
Admission weight for height (Z)	−2·5 (1·1)	−3·0 (0·7)	−2·2 (1·0)	−1·6 (0·9)
Discharge weight for height (Z)	+0·1 (0·6)	−0·6 (0·7)	+0·1 (0·5)	+0·1 (0·6)
Time admission to baseline study (days)	11 (3)	8 (3)	9 (2)	13 (6)
Time baseline to discharge study (days)	29 (10)	34 (10)	26 (11)	26 (7)

Z=SD scores from the NCHS standard height of a child of the same age and weight for a child of the same height.

fortified with vegetable oil (corn or coconut) to give an energy density of 5·7 MJ/kg, vitamins, and minerals.[13]

COMPARISON GROUPS

Eleven children who were resident in a local children's home were studied as a control group. Eight previously malnourished children, who had had grade 0 or 1 steatosis at discharge, were also studied between 32 and 162 days after discharge, as a further comparison group. Each of these children was assessed as clinically healthy; they were anthropometrically within 1 SD of the median weight of a child of the same height and sex (National Center for Health Statistics (NCHS) standards).

CONSENT

Informed consent was obtained from each child's parent or guardian. The study was approved by the ethics committees of the University of the West Indies and of the Ministry of Health, Jamaica.

ULTRASOUND PROCEDURE

Each study child had ultrasonography performed on three occasions:

(1) Within 48 hours of admission (admission);

(2) As soon as the acute signs of malnutrition had resolved but the child had not yet gained any appreciable weight (baseline). This was defined as the first point in time at which the children were oedema free and had gained weight at a rate of 5 g/kg/day, for three consecutive days.

(3) Once the child had regained weight to within 1 SD of the median weight of a child of the same sex and height (NCHS standards) and had spontaneously reduced its appetite so that it was gaining weight at a normal rate (discharge).

Control children were studied once.

On each occasion, hepatic ultrasonography was performed using an Ultramark IV machine (Advanced Technology Laboratories) with a 5 MHz probe, by the same investigator (JFD). Photographic prints were obtained at each study; these were randomly coded, shuffled, and sent to England. The extent of hepatic steatosis was assessed from the coded prints alone, independently and blindly with respect to the child's diagnosis and the stage of recovery at which the study was performed, by a single assessor (EJA). The assessment was based on previously published criteria,[10] modified to provide a numerical severity score. This ranged from 0=normal to 5=very severe. Mild steatosis was recognised by a slight increase in liver echogenicity and a slight exaggeration of the echo discrepancy between liver and kidney (grade 1). Moderate steatosis was accompanied by loss of echoes from the walls of the portal veins, resulting in a featureless appearance, with a degree of posterior beam attenuation and a greater discrepancy between the liver and kidney echo pattern (grade 3). Very severe steatosis was determined by a still greater degree of posterior beam attenuation, loss of echoes from most of the portal vein, and a marked discrepancy between liver and kidney (grade 5)[10]; grades 2 and 4 had intermediate appearances.

Assessment of liver size was made by measuring the liver span, in the mid-clavicular line, using ultrasonographically determined surface markers. This measurement was standardised by expressing liver span as a percentage of body length. Span was not recorded in the control children.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Systat Software package (Systat Inc). Non-parametric statistics (Kruskal-Wallis and Friedman analysis of variance (ANOVA) and Mann-Whitney tests) were used for comparison of the degree of hepatic steatosis, as the severity score is not a continuous variable. Parametric statistics (ANOVA) were used for analysis of the liver span data after testing for normality.

A smoothing algorithm[14] was used to assess the rate of disappearance of liver fat graphically; the program fits a line through a set of points using distance weighted least squares quadratic regression. A tension of 0·1 was used. The resulting lines are similar to those produced by the method of Cleveland.[15]

Results

STUDY CHILDREN

Children without oedema (undernutrition and marasmus) were older than the oedematous (marasmic-kwashiorkor and kwashiorkor) children ($p<0·05$), and a higher proportion were male (table 1). The undernourished children were not as stunted as the marasmic children: however, they were just as wasted (deficit in weight-for-height); this indicates that the two non-oedematous groups had had similar recent nutritional insults. The times between the three studies were not different among the groups.

All three assessments were made on 51 of the 55 children: one child was considered too ill for ultrasonography to be performed at admission; two children died (one with marasmic-kwashiorkor after the admission, the other, with kwashiorkor, after the admission and baseline study); one child was inadvertently discharged before the final ultrasound.

HEPATIC STEATOSIS

The results are shown in fig 1. Control subjects, with one exception, had a steatosis grade of 0 or 1. The exception was a 16 month old boy, resident in the children's home, who was assessed as having grade 2 steatosis. Clinical examination of the child and conventional liver function tests were normal. The previously malnourished children, studied at follow up also had either grade 0 or grade 1 steatosis.

At admission 51 of the 54 children had evidence of fat in their livers: the one child who was too ill for assessment, at this time, had grade 5 steatosis at baseline. For each of the diagnoses, at both admission and baseline, the extent of

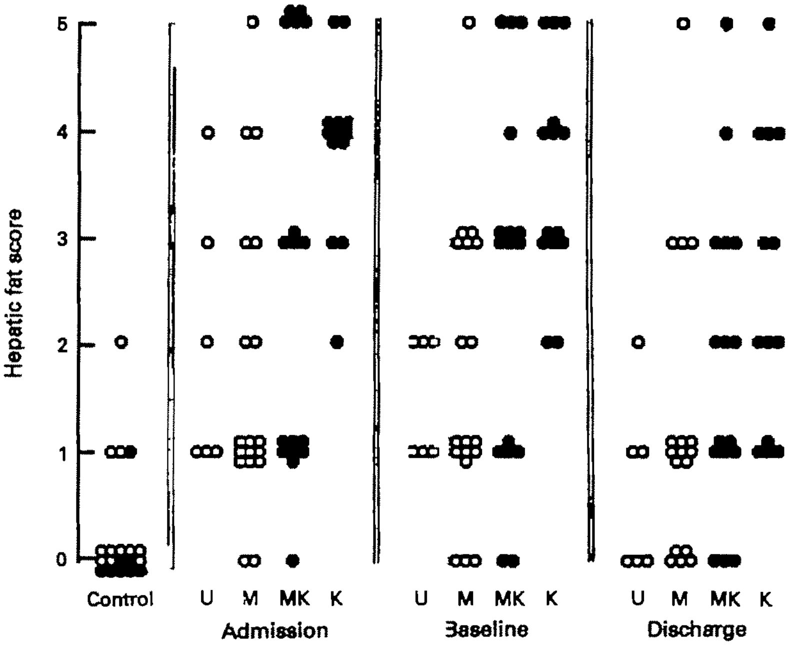

Figure 1 The hepatic fat score in control and previously malnourished children and in groups of malnourished children on admission, after resuscitation but before any appreciable weight gain (baseline), and at discharge. The control open dots are for children from a children's home, the control closed dots are for previously malnourished children. For the malnourished groups: U, undernutrition, M, marasmus, MK, marasmic-kwashiorkor; K, kwashiorkor; open dots, non-oedematous malnutrition; closed dots, oedematous malnutrition Each dot represents a separate subject.

hepatic steatosis was significantly greater than the controls (fig 1) (p<0·01). The extent of hepatic steatosis was different within the four groups, at each stage of the study (p<0·02). The grade was greater in children with oedematous malnutrition than non-oedematous and greater in those with kwashiorkor than those with marasmic-kwashiokor (p<0·0001). Children without oedema, however, had appreciable hepatic steatosis (fig 1). Eight of 17 children with marasmus and three of six with undernutrition had an hepatic ultrasound severity score ≥2 both at admission and at baseline.

RECOVERY OF FATTY LIVER

Figure 2 shows the distance weighted least squares quadratic regression lines of the hepatic steatosis grade, with time from admission, by diagnosis. Over the time of observation there was a gradual reduction in the fat score, so that by discharge there were significantly lower scores (p<0·01) in each category (fig 1). However, only three of 29 children with an admission diagnosis of oedematous malnutrition and eight of 22 with previous non-oedematous malnutrition had attained a score of 0 by discharge. Furthermore, about one quarter of both the oedematous (seven of 29) and non-oedematous children (five of 22) had the same score (≥2) at baseline and at discharge; during rehabilitation, these children had not mobilised sufficient fat to alter the abnormal ultrasonographic appearance of their livers. If the intervals between the severity grades are approximately equal and the mobilisation of fat is exponential,[2] then a rate constant (K) for mobilisation of liver fat can be calculated for each of the children that had a score of greater than 0 at discharge. These constants, calculated between baseline and discharge, are shown in table 2. Overall only 1·4% of the liver fat was mobilised each day. There were no statistical differences between the rate constants of any of the diagnostic categories.

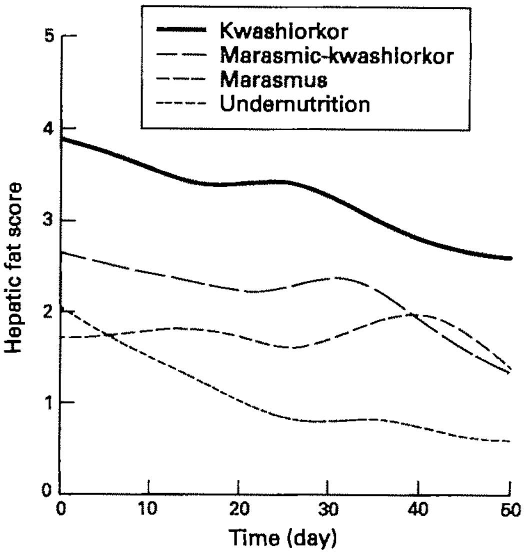

Figure 2 The distance weighted least squares quadratic regression lines of the hepatic fat score in the four groups of malnourished children with time.

Table 2 Rate of mobilisation of liver fat during recovery from malnutrition; values are mean (SEM)

Group	No in group	Rate constant (/day) baseline to discharge
Undernutrition	3	0 013
Marasmus	12	0 008 (0 004)
Marasmic-kwashiorkor	11	0·019 (0 007)
Kwashiorkor	13	0 016 (0·005)
Non-oedematous	15	0 009 (0 004)
Oedematous	24	0 017 (0 004)
All patients	39	0·014 (0 003)

None of the groups were significantly different

LIVER SPAN

The liver span was about 1 cm larger in oedematous than non-oedematous children at both admission and baseline; these differences were significant (table 3). There was no significant effect of time of study on the liver span and no interaction between time and diagnosis. Overall, there was no relationship between the degree of hepatic steatosis and the size of the liver. When the different time points were analysed separately there was a weak positive correlation between the liver span and the degree of hepatic steatosis at admission (Spearman's rho=0·308, p<0·05); the relationship was not significant at baseline or discharge.

Table 3 Liver size[†] in malnourished children; values are mean (SD)

	Undernutrition (n=6)	*Marasmus (n=18)*	*Marasmic-kwashiorkor (n=17)*	*Kwashiorkor (n=14)*
Admission	8·1 (2 3)	8·1 (1·3)	8·9 (2·1)	9·5 (1·8)
Baseline	8·2 (0·9)	7 8 (1 0)	8 5 (1 7)	9 2 (1·1)
Discharge	9·2 (1 2)	7 6 (1·3)	8 3 (1·1)	8·3 (1·0)

[†] Liver size measured as liver span (cm)×100/height of child (cm)

Discussion

The precise pathogenesis of fatty liver is unknown. Several theories to explain its occurrence in kwashiorkor have been proposed: endocrine abnormalities,[16] increased fat synthesis,[8] redistribution from adipose tissue,[17] reduced lipoprotein synthesis,[18 19] abnormalities of lipoprotein lipase,[20] and peroxisomal dysfunction,[21] have each been put forward as playing a part. If the child recovers the fat disappears apparently without any long term sequelae.[22]

The extent of liver fat in the present population was not measured directly; however, the cases were similar to those studied by Waterlow in whom the median amount of fat was about 30–35% of total liver wet weight.[2] The distribution of his cases in % fat classes and of our cases into grades was also similar. Thus, we would anticipate our grade 4 to correspond to Waterlow's 30–40% fat and our grade 5 to more than 40% fat. Although this is an assumed correspondence between the grades and chemical composition, the extent of liver fat in these children is likely to be much greater than in the adult population in which the method was quantitatively validated. Nevertheless, our assessment was made in a masked fashion by an experienced ultrasonographer who had no knowledge of the subjects.

The study confirms the frequency of fatty liver in children with oedematous malnutrition, although there are a few oedematous children without appreciable fatty liver (3–6%). However, our results also show that fatty liver is *usually* present in marasmus and undernutrition—non-oedematous forms of malnutrition. In the Wellcome classification of malnutrition,[11] nutritional oedema is *equated* with kwashiorkor; however, fatty liver is part of the *clinical syndrome* of kwashiorkor.[1] The finding, that fatty liver is frequently present in marasmus, blurs the differences between the Wellcome definitions of kwashiorkor and marasmus. Clearly, the Wellcome classification is useful, among other things, for studies of the pathogenesis of oedema whereas it is misleading if used for studies of the pathogenesis of fatty liver.

The rate of clearance of the fat in the liver was remarkably slow, with up to one quarter of children not apparently metabolising any of the fat in their livers during recovery. Our figure of 1·4%/day is in broad agreement with Waterlow's two estimates of 5·5%/day and 0·9%/day, using different assumptions. If a 7 kg child has a 400 g liver, with 35% wet weight as fat (20 g hepatic fat/kg) and he mobilises 1·4%/day then only 10·6 kJ/kg/day (2·5 kcal) is coming from hepatic fat. Even if the higher of Waterlow's estimates is used, less than 40 kJ/kg/day is supplied from hepatic fat. This is a relatively tiny fraction of the energy consumption of these children, who become markedly hypermetabolic during their period of rapid weight gain.[23] Their dietary energy supply is closely related to their rate of recovery[24 25]: the children frequently consume 800 kJ/kg/day with 60% of this energy coming from fat; thus, children may oxidise 13 g fat/kg/day.[25] Clearly, during recovery, they do not have a metabolic constraint on fat oxidation. Equally, the children increase their plasma lipoproteins within three to five days of admission to supranormal concentrations[26]: there does not seem to be a difficulty with lipoprotein synthesis during recovery. Under these circumstances, one would expect the fat in the liver to be rapidly consumed. However, our data, and those of Waterlow[2] indicate that the fat is mobilised slowly. The defects that form the bases for the current theories of the pathogenesis of fatty liver in malnutrition are quickly corrected during recovery from malnutrition: they are inadequate to explain the phenomenon of persistent hepatic steatosis.

There was no overall association between liver size and liver fat despite the extensive steatosis at each stage of recovery. Our results emphasise that there is often severe fatty liver in malnutrition without significant hepatomegaly.

Ultrasound can be used non-invasively and repeatedly to assess fatty liver in further studies of malnutrition. Ethical constraints preclude the use of liver biopsy in children that are relatively well. No data exist, therefore, on the extent of fat in the liver of 'normal' and mild or moderately malnourished children in developing countries. Our results show that fatty liver occurs in undernourished children and even in one of our control children, despite normal liver function tests. It is possible that the prevalence of fatty liver in children in the developing world is greater than is generally believed.

This work was supported by the Wellcome Trust We are grateful to Professor G Serjeant, MRC Sickle Cell Laboratories, University of the West Indies for allowing us access to the ultrasound machine and to Dr H Mohammed for his help Drs R Wilkes and D T Simeon gave valuable statistical advice

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Methotrexate for severe asthma

Despite the major advances in the treatment of asthma that have been made in the last quarter of a century or so there are still some patients who have severe and even life threatening asthma, although receiving maximal current conventional therapy, and others who suffer the ill effects of regular high dose steroid treatment. Can anything else be done to help such patients? There have been reports of improvement in adults with severe asthma after treatment with methotrexate and a recent paper from Kansas City, Missouri (Salomon Guss and Jay Portnoy, *Pediatrics* 1992;**89**: 635–9) gives details of a small uncontrolled trial in children.

Five girls and two boys aged between 3 and 14 years were treated. All had severe asthma and were receiving regular oral prednisone in doses ranging from 30 mg on alternate days to 60 mg daily in addition to inhaled treatment with salbutamol, sodium cromoglycate, and beclomethasone, and oral theophylline. Two of the seven patients had frequent emergency department visits and hospital admissions but one of them was thought to be non-compliant with treatment. Methotrexate was given in a starting dose of 2·5 mg once a week and the dose was increased by 2·5 mg every four weeks to a maximum of 17·5 mg in two patients, 12·5 mg in three, and 7·5 mg in one. One patient was unable to tolerate the drug and had only two doses.

No patient showed any improvement in the asthma in the first three months of methotrexate treatment but eventually three patients came off steroids and two were able to take a much reduced dose. Data are provided about spirometric measurements before and during treatment but they are difficult to interpret because we are not told when the values given were obtained and whether they represent an average over a period of time or single recordings. One patient showed no response after treatment for six months. One 9 year old had all her treatment stopped by her family when her asthma improved after four months of methotrexate. Two children apparently deteriorated and improved again when the course of methotrexate was interrupted and restarted.

The authors try very hard, in my opinion too hard, to make a case for methotrexate. They emphasise the toxicity of steroids in comparison with methotrexate in a quite arbitrary fashion and their assessment of their results does not seem to be totally unbiased. For instance they claim that methotrexate led to fewer emergency visits and admissions to hospital when it is quite clear from their data that there was no significant effect in these respects. They point out in high falutin terms that the study was uncontrolled and therefore the value of the drug remains uncertain but they encourage doctors to try the drug on a 'give it and see' basis. There is serious concern about the potential toxicity of methotrexate with pneumonitis, pulmonary fibrosis, and hepatic fibrosis being the main worries. In the present state of knowledge it seems to me that to encourage anything other than a strictly monitored controlled trial would be hard to justify. As far as treating individual patients is concerned, if there is a flag indicating 'proceed with extreme caution' it would seem appropriate to wave it vigorously at this point.

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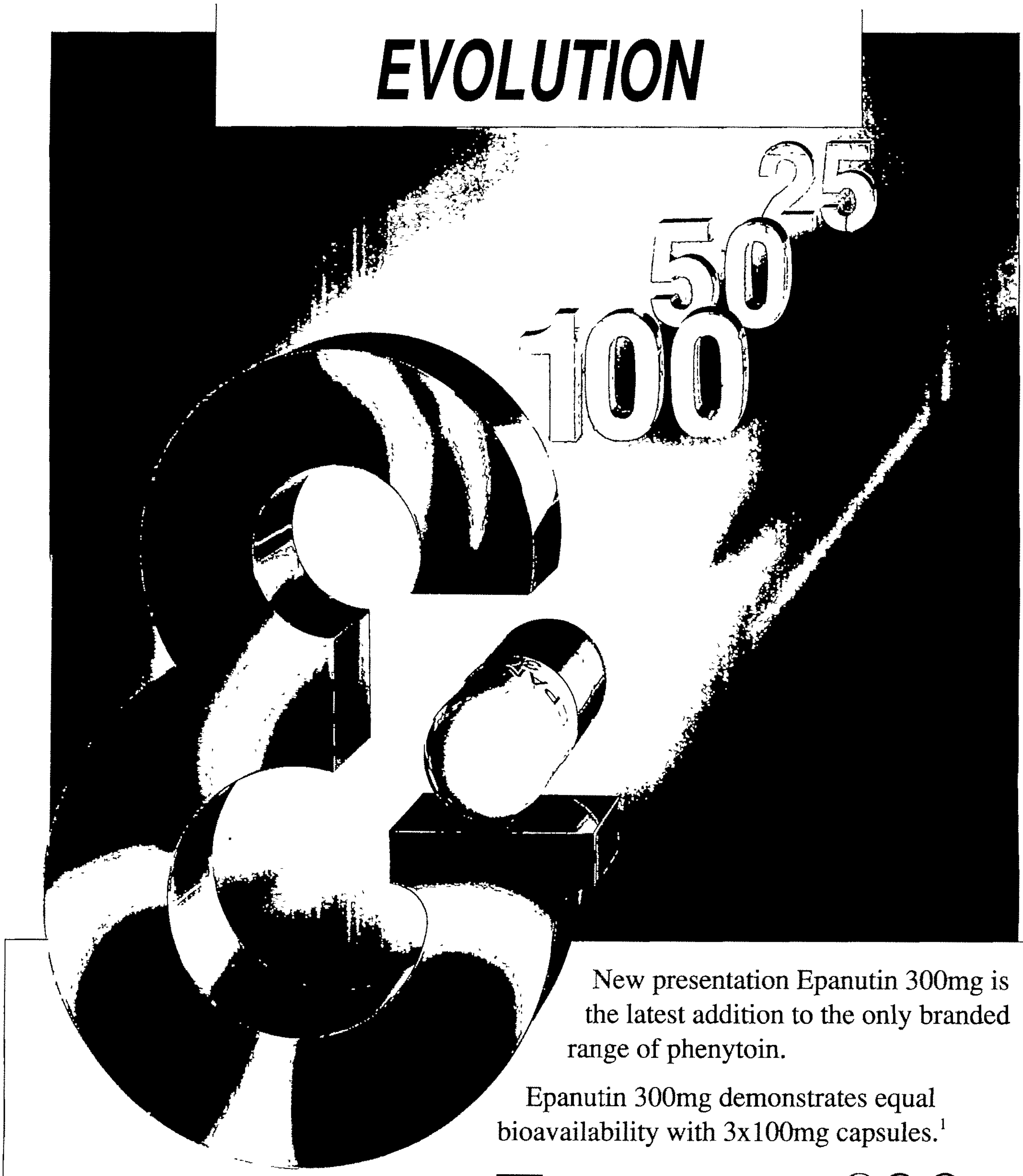

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Delayed surgery for congenital diaphragmatic hernia: neurodevelopmental outcome in later childhood

Mark Davenport, Elise Rivlin, S W D'Souza, A Bianchi

Abstract

The long term neurodevelopmental outcome was assessed in 23 survivors born with congenital diaphragmatic hernia who had been managed by an elective delay in surgical repair after a period of stabilisation. This cohort was treated in one neonatal surgical unit between 1983 and 1989 by a single team of surgeons and anaesthetists. All children underwent comprehensive neurological, developmental, and anthropometric assessment at a mean age of 56 (range 18–94) months. Two children (9%) had major disability (one with hemiplegia and one with a lower limb monoplegia) and two further children had minor disabilities (one had partial sightedness and squint, the other squint only). The mean developmental quotient (DQ) for the group was 108 (SD 10·8) and none had developmental delay (defined as DQ <70). Infants who had spent more time in hospital, or had had a longer duration of ventilation, tended to have lower weights and lower occipitofrontal circumference centiles in later childhood. Preoperative stabilisation and delayed surgery for congenital diaphragmatic hernia is not associated with an impaired neurodevelopmental outcome.

(*Arch Dis Child* 1992;67:1353–6)

During the past eight years there has been a radical change in the surgical management of infants with congenital diaphragmatic hernia (CDH).[1–5] Thus, in several centres, there has been a move away from the traditional policy of emergency surgical repair toward a policy of a delay in surgery until the infant is stable. This approach was instituted because of a realisation that the high mortality rates (of about 50%) were essentially related to the severe pulmonary hypoplasia and the associated raised pulmonary vascular resistance with marked right-to-left shunting. It had been appreciated that emergency surgical repair of the diaphragm with return of bowel into the abdomen had not helped survival, and may indeed have affected it adversely.

In 1983 the policy on the neonatal surgical unit at St Mary's Hospital, Manchester, was altered principally to emphasise the management of the pulmonary hypoplasia. The infant's oxygen requirements were minimised and attempts were made, both to use available lung tissue to maximum effect, and to reduce the right-to-left shunt. Surgery was eventually offered, only after the acute phase, to those with stable pulmonary circulations whose only remaining reason for ventilation was the presence of a diaphragmatic hernia with bowel in the pleural space. Management included neuromuscular paralysis and ventilation and correction of acid–base balance or haemodynamic disturbances.[1]

Though earlier reports of delayed surgery for diaphragmatic hernia have been encouraging,[2–5] with a trend towards improved survival, there has been no published study on the long term effects of this delayed surgery policy. This protocol implies an elective period of prolonged intensive care and resuscitation which, although apparently achieving greater survival rates, might be associated with an increased incidence of cerebral damage and later handicap. In the present study we have retrospectively examined our population of survivors after surgery with particular regard to their growth and neurodevelopmental outcome.

Patients and methods

The neonatal surgical unit at St Mary's Hospital, Manchester, is a regional centre receiving referrals from the north west of England (approximate birth rate 60 000 per annum). There were 23 children who had surgery for CDH between 1983 and 1989 and who lived within the Greater Manchester area. They attended outpatient clinics for neurodevelopmental and anthropometric assessments which were carried out by a paediatrician (SWD'S) and a child psychologist (ER). The developmental assessment by Griffiths's mental development scales (GMDS)[6] was carried out by the child psychologist who was unaware of the perinatal history or neonatal complications.

Clinical and intensive care records were examined for the time to surgery, duration and type of ventilation (intermittent positive pressure ventilation (IPPV) or continuous positive airway pressure), blood gas and pH measurements, complications such as persistent fetal circulation and the use of certain drugs, for example, tolazoline.

Using the GMDS a general development quotient was calculated from the mean of six subquotients (locomotor, personal/social, hearing and speech, eye–hand coordination, performance, and practical reasoning). Age to first walking was also noted. Anthropometric data was collected from each child and included height, weight, occipitofrontal head circumference, and triceps and subscapular skinfold thickness. This was expressed according to the appropriate age corrected centile group using charts prepared by J M Tanner and

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Table 1 Perinatal cerebral ultrasonography and neurological disability in four survivors following diaphragmatic hernia repair

Patient No	Ultrasound brain scan	Follow up		
		GMDS DQ	Locomotor SQ	Neurological findings
1	IVH, left hemisphere, ischaemic change	85	59	Right hemiplegia, reduced head growth walked at 18 months
2	IVH, dilated ventricles	123	133	Normal
3	Right and left subependymal-haemorrhage	100	106	Partially sighted and squint; walked at 24 months
4	Normal	108	114	Left lower limb monoplegia

DQ=development quotient; SQ=subquotient; IVH=intraventricular haemorrhage.

R H Whitehouse, and D Gairdner and J Pearson (Castlemead Publications, Herts).

Data were expressed as mean (SD) or where there was a significantly skewed distribution as median (range). Similarly, differences in group means were analysed by the unpaired Student's *t* test or the Mann-Whitney U test, as appropriate. To investigate the relationship between perinatal variables and outcome, simple bivariate correlations were used in most instances (a Spearman rank correlation coefficient (r_s) was used if either variable was non-parametric). A p value of <0·05 was regarded as significant.

Results

All 23 infants had symptomatic diaphragmatic hernia (21 left sided, one right sided, and one bilateral) presenting on the first day of life and had elective surgery once the pulmonary circulation had stabilised.

Twenty two of 23 infants were born at term with a mean birth weight of 3080 g (SD 540); the remaining infant was preterm and born at 33 weeks' gestation with a weight of 1700 g (<3rd centile). Surgery was performed at a mean age of 72 hours (range 5–120 hours). All infants were ventilated before and after surgery (median duration of IPPV was 7 days, range 1–35 days). Neuromuscular paralysis was used in 21 (91%) of 23 infants. Tolazoline and dopamine were used in six (26%) and two (9%) infants respectively. Persistent fetal circulation was diagnosed clinically in six (26%) infants. Cerebral ultrasound scanning was carried out in all the infants and a structural cerebral abnormality was detected in three (13%) (table 1). The median duration of hospital stay was 34 days (range 12–110 days). Table 2 gives details of perinatal blood gas analysis and ventilation variables in 23 infants.

Children were examined at outpatient clinics at a median age of 56 months (range 13–94 months). Table 3 shows the neurodevelopmental outcome. Neurological (including both hearing and vision) examinations showed no abnormality in 19 (82%). Of the remaining infants, two (9%) had major disability (one had a lower limb monoplegia and one, right hemiplegia), and a further two had minor abnormalities (one had partial sightedness and squint; the other had squint alone).

Table 2 Blood gas analyses and ventilation variables in 23 infants with congenital diaphragmatic hernia

	pH (min/max)	Minimum oxygen tension (kPa)	Maximum carbon dioxide tension (kPa)	IPPV (days)	CPAP (days)	Maximum fractional inspiratory oxygen (%)
Mean	7·1/7 51	6·0	9·2	NA	NA	NA
SEM	0·19/0 05	0·35	0 5[illegible]	NA	NA	NA
Median*	NA	NA	NA	7	1	80
Range	(6 7–7·4)	NA	NA	(1–35)	(0–5)	(40–100)

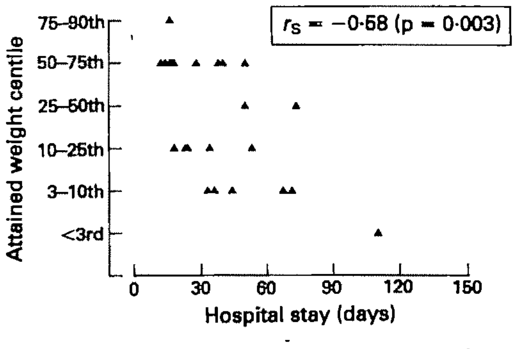
*A median (range) value is quoted when the variable is significantly skewed.
CPAP=continuous positive airways pressure; NA=not applicable

The mean (SD) GMDS general quotient for the group (n=23) was 108 (10·8); range 85–133. This was derived from six subquotients: locomotor, 110 (18·3); personal and social, 113 (11·2); hearing and speech, 110 (14·4); eye-hand coordination, 107 (13·1); performance, 104 (13·8); and practical reasoning, 107 (14·3). Analysis of variance did not show any significant difference between these subquotient means (F ratio=1·14; p=0·34). There was no significant correlation between the GMDS general quotient and any perinatal variable (time to surgery, period of IPPV, blood gas analysis, length of hospital stay). The median age of walking was 12·5 months (range 10–24). There was no significant correlation between the GMDS general quotient or the GMDS locomotor quotient and the age of walking. There was moderate correlation between the age of walking

Table 3 Neurodevelopmental outcome in 23 survivors after delayed repair of congenital diaphragmatic hernia

Index	Mean (SD)	Median (range)
Time to walk (months)	NA	12 5 (10–24)
GMDS quotient	108 (10 8)	NA (101–114)
*Subquotients**		
Locomotor	110 (18·3)	NA (100–24)
Personal and social	113 (11·2)	NA(106–120)
Hearing and speech	110 (14·4)	NA (99–119)
Eye–hand coordination	107 (13·1)	NA (98–115)
Performance	104 (13 8)	NA (97–114)
Practical reasoning	107 (14·3)	NA (97–120)

Analysis of variance (F ratio 1·14, p=0 34); NA=not applicable



Achieved weight centile at follow up versus duration of hospital stay in 23 children after diaphragmatic hernia repair.

and length of IPPV (r_s=0·41, p=0·05). Persistent fetal circulation in the neonatal period (n=6) did not influence attained GMDS (p=0·1) or the age of first walking (p=0·77).

Height, weight, and occipitofrontal head circumference were all expressed according to age related centile charts. Thus, of 23 children, one was below the 10th centile for height, six below the 10th centile for weight, and three below the occipitofrontal 10th centile. There was significant inverse correlation between attained weight centile and both duration of IPPV (r_S=−0·42, p=0·04) and duration of hospital stay (r_S=−0·58, p=0·003; figure). Similarly there was an inverse correlation between attained occipitofrontal centile and duration of IPPV (r_S=−0·41, p=0·05). There was no relationship between the attained height centile and any perinatal variable.

Discussion

CDH is a condition with a high mortality rate, even when treated within specialised neonatal units.[7] [8] Antenatal diagnosis gives no indication of eventual outcome. In fact, mortality rates for CDH may actually increase because antenatal diagnosis allows for planned delivery, close to the surgical unit, of non-survivors with severe pulmonary hypoplasia.[9]

The preoperative and postoperative course in these infants is characterised by episodes of reversion to the fetal type of circulation with rapid swings in blood pH, blood pressure, and blood oxygen tensions. While the long term effects on respiratory function have been well documented in children with a history of CDH, their neurodevelopmental outcome is not clear.

There have been several recent studies on neurodevelopmental outcome following a period of extracorporeal membrane oxygenation (ECMO) in the neonatal period.[10–12] Thus Adolph *et al*, reviewed 57 children who had survived after ECMO for various conditions including CDH (although the proportion was not specified).[10] Using Bayley scales of infant development (mental development index (MDI) and a psychomotor development index (PDI)) they found that 25% scored less than normal (defined as under 85) on the MDI while 12% scored less than normal on the PDI. There was one child (2%) with a major neurological abnormality. If infants receiving ECMO are from a similar population to our own (that is, sustaining severe episodes of hypoxia, acid-base disturbances, and difficult ventilation) then the neurological outcome reported here appears to be similar.

The early neurodevelopment outcome in children after various types of neonatal surgery (but without ECMO) has been the subject of a previous study.[13] In this, there was a significant reduction in the attained development quotient at 1 year of age in those children who had surgery as compared with control children who did not. This occurred in a heterogeneous group of infants of different gestational ages in whom surgery was carried out for various conditions such as abdominal wall defects and intestinal atresias. This study also showed that the severity of illness within the first month of life and the length of hospital stay might be followed by reductions in attained developmental scores.[13] A longer term (mean age of testing 10 years) psychosocial and growth study has previously been reported in children with neonatal repair of abdominal wall defects and imperforate anus.[14] These authors found a normal distribution of both anthropometric indices and developmental achievement in their population of 56 children.

The first few days of life represent a critical period during which the child with CDH is at risk of developing damage from hypoxia, hypercapnia, and acidosis.[15] [16] It has recently been determined in preterm infants (less than 32 weeks) that the presence of periventricular leucomalacia (presumed to be due to ischaemic brain injury) diagnosed in the first two hours of birth may have been acquired either antenatally or during the birth process.[17] Other studies have suggested that most hemiplegias in term infants may, in fact, be of prenatal origin.[18] In the present study one child had a hemiplegia and an abnormal brain scan (patient 1, table 1). This child did require a prolonged period of 120 hours ventilation before surgery. The other child with a monoplegia had no obvious clinical complications which may have predisposed to brain damage. Routine ultrasound brain scans during the neonatal period had shown no abnormality. Thus, the precise time and reason for brain damage in this child is not clear. Two further infants had abnormal brain scans (table 1). One developed partial sightedness, a squint and some delay in walking, whereas the other had no detectable abnormality in later childhood.

The period of hospitalisation in our infants may have influenced their subsequent growth. The present findings suggest that infants who spent more time in hospital or required a longer duration of ventilation tended to follow a lower weight centile and a lower occipitofrontal centile in later childhood. Whether this relationship is due to the severity of their original condition or to other factors, such as early nutrition, remains speculative. Insufficient early nutrition may have played a part, as it is well known that the quality and quantity of the early diet can have a significant later effect on weight, length, and head circumference.[19] It is possible that the length of stay was not in itself significant, but rather a reflection of the child's failure to establish a satisfactory weight gain. Thus, careful attention to sustained nutrition (parenteral or enteral) from an early stage might have a significant impact on long term physical outcome.

In a previous study[1] we have shown that an initially conservative policy designed to overcome the life threatening consequences of pulmonary hypoplasia and raised pulmonary vascular resistance, with subsequent diaphragmatic surgery when stability has been achieved, is associated with improved survival. In this study we show that this improvement does not occur at the expense of a poor neurological outcome or development delay in the survivors. There is a suggestion from our study that somatic growth in survivors may be affected and, in particular, the ability to gain weight. The actual cause for this is unclear and requires further careful evaluation.

We thank Mr S J J Cohen, Miss C M Doig, and Mr D S C Gough for allowing us to study their patients.

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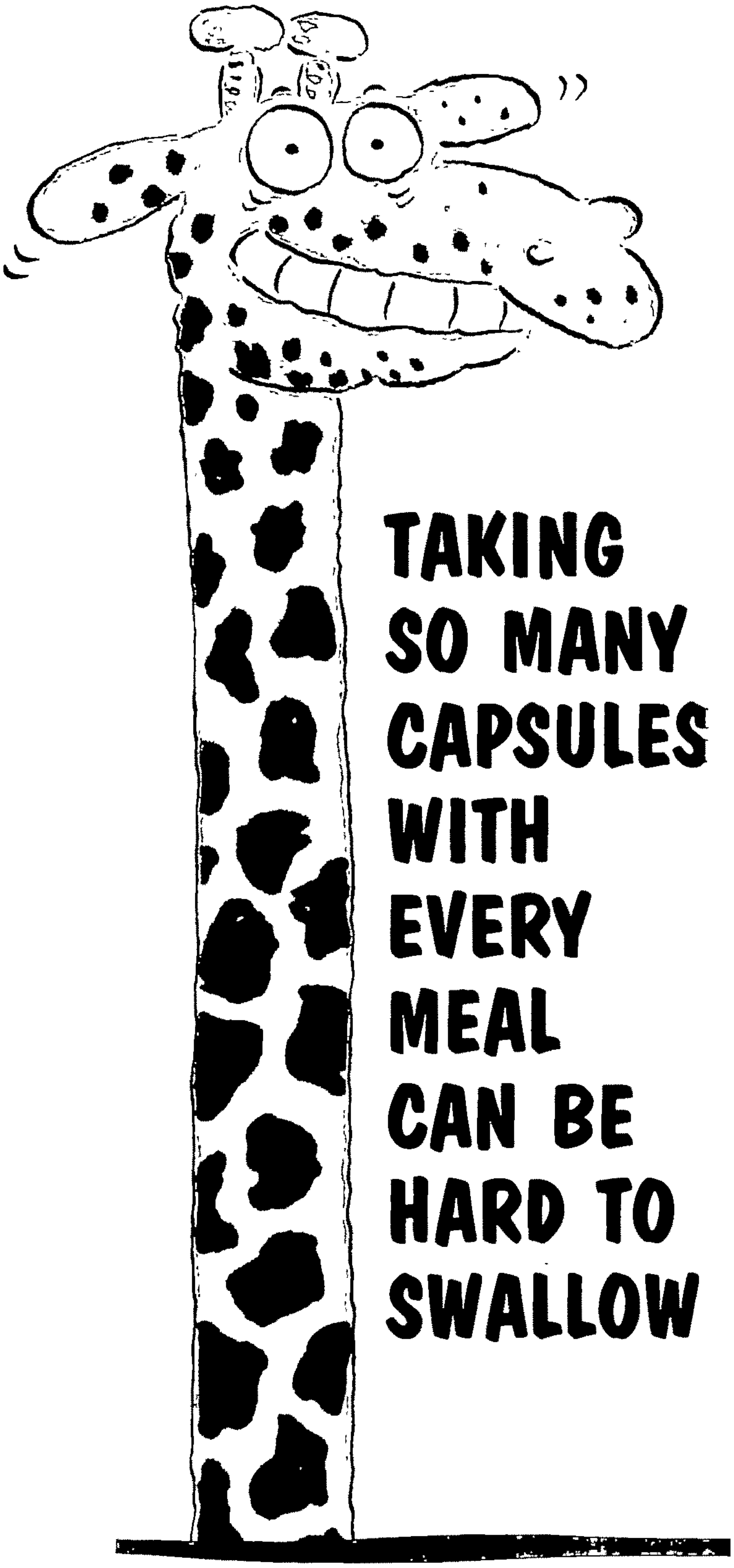

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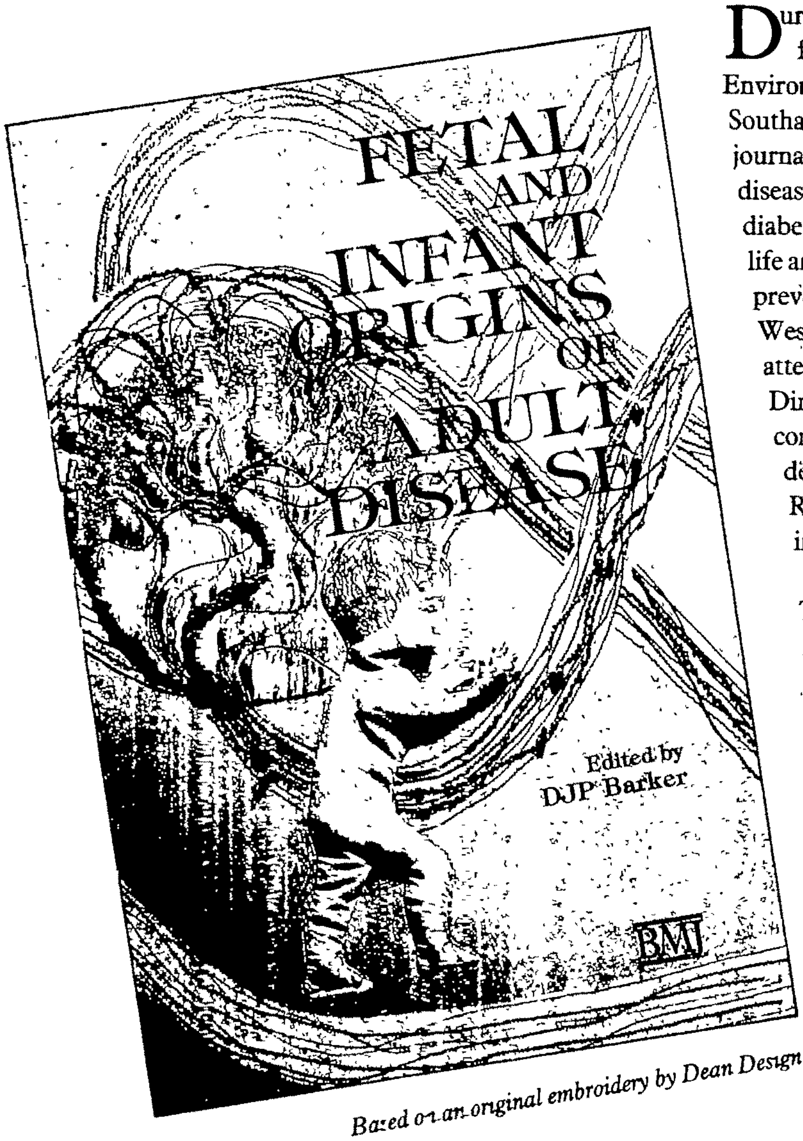

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Adult height in constitutionally tall stature: accuracy of five different height prediction methods

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Abstract

The accuracy of height predictions at various ages based on five different methods (Tanner-Whitehouse mark I; Tanner-Whitehouse mark II; index of potential height; Bayley-Pinneau; Roche-Wainer-Thissen) was compared at yearly intervals with final height achieved in 32 boys (78 predictions) and 100 girls (227 predictions) with constitutionally tall stature. The boys were initially seen at a mean (SD) chronological age of 12·5 (3) years whereas the mean chronological age in girls was 11·8 (2·1) years.

In tall boys Tanner-Whitehouse mark II gives a good estimation of final height up to the bone age of 13 years with a mean overestimation of 1 cm. The overestimation of final height is higher in the bone age groups 13–14 years (2·7 cm) and 14–15 years (3·4 cm) mainly due to the tall boys with a height greater than 3 SD scores. Up to the bone age of 12 years the final height is massively overestimated by the Bayley-Pinneau method but this method give relatively accurate estimations thereafter. The estimated confidence limits are large (±8 cm) for the two methods up to a bone age of 15 years.

In tall girls the Tanner-Whitehouse mark II method was accurate from bone age nine to 12 years but overestimated final height in the bone age groups 12–13 years and 13–15 years by a mean of 1·8 and 1·4 cm respectively. The Bayley-Pinneau method overestimated final height in the bone age groups 12–14 years whereas the height predictions are accurate thereafter. Up to a bone age of 13 years the estimated confidence limits for the two methods are large, ±7 cm, but tend to improve thereafter.

It is concluded that there is no best or most accurate method for predicting adult height in tall children. There are methods of first choice differing with respect to sex and bone age. In addition, correcting factors may improve their accuracy and correct their tendency to overestimate or underestimate adult height.

(*Arch Dis Child* 1992;67:1357–62)

In constitutionally tall children the prediction of adult height is a major parameter for deciding whether or not any treatment should be given. Methods of prediction of adult height are mainly based on growth data from children of normal stature selected more or less at random and followed from infancy to adulthood.[1–6] To date only the Tanner-Whitehouse mark II equation has included samples of tall children.[7, 8] Thus applying standard equations for determining adult height to children with growth disorders may not give accurate results.

If treatment is given an accurate prediction of adult height is an important element in monitoring its influence on growth and skeletal maturation. The evaluation of the extent to which any given treatment has reduced the adult height is based on the difference between the predicted and attained adult height. The criteria for a good prediction method are reasonable accuracy over a large age range, small prediction error, and, if possible, validity for tall and for normal children.

This study was performed to investigate and re-evaluate retrospectively growth data deriving from untreated tall children who were referred to our growth clinic at the paediatric department in Berne and whom we followed up until their adult height was achieved.

Patients and methods

PATIENTS

Thirty two boys and 100 girls entered the study. At referral the mean (SD) age was 12·5 (3) and 11·8 (2·1) years in boys and girls respectively. The mean (SD) bone age ratings were 13·0 (2·6) years in the boys and 12·1 (1·8) years in the girls according to Greulich and Pyle. All the subjects were followed up until adult height was achieved.

The criteria for inclusion were tall stature (greater than two SD scores according to the first Zurich longitudinal study of growth and development[10]) without any disorder explaining the tall stature; the subjects were in good health.

A total of 78 (boys) and 227 (girls) predictions of adult height were performed in the 32 boys and 100 girls at yearly intervals. Adult height was assumed when either two height measurements within six months were equal or the bone age estimated by the method of Greulich and Pyle[9] was $\geqslant$18·25 years in boys and $\geqslant$16·75 years in girls representing the achievement of 99·8% of their adult height. The remaining growth potential of 0·2% was judged to be within a possible error of measurement.

The subjects were divided into two groups, one consisting of patients with a height of $\geqslant$3 SD scores[10] and another of patients with a height >2 SD scores and <3 SD scores.[10] In adddition subjects with an accelerated bone age of more than two years were analysed separately and reported whenever the data of the distinct groups were different.

The overall mean adult height in boys was 194·0 (2·6) cm. Only four of the 32 boys initially had an accelerated bone age of more than two years and their median adult height was 193·7 cm.

The overall mean adult height in girls was 177·3 (2·2) cm. Seventeen of the 100 girls initially showed an accelerated bone age of more than two years and their mean adult height was 174·2 cm. In addition four girls presented a retarded bone age (≥2 years) when they were first seen and reached the mean adult height of 180·6 cm.

HEIGHT MEASUREMENT

All measurements were taken using a Harpenden stadiometer with the technique of gentle upward pressure applied under mastoid processes to stretch the child to maximum stature. Measurements were performed by the staff of the paediatric endocrine clinic and checked by a paediatric endocrinologist. The height data are expressed as SD scores for chronological age using the tables derived from the first Zurich longitudinal study of growth and development.[10] We measured three tall children on three different occasions to define the intra-assay and interassay coefficients of variation. The intra-assay coefficient of variation was 0·08, 0·06, and 0·09% at 164·7, 176·3, and 186·5 cm respectively. The interassay coefficient of variation was 0·29, 0·31, and 0·34% at 164·7, 176·3, and 186·5 cm respectively.

BONE AGE

Radiographs of the hand and wrist were taken and rated according to the methods described by Greulich and Pyle[9] and by Tanner *et al.*[2 7] In this study all the bone ages were analysed by RT.

When using the Greulich and Pyle method[9] the carpal bones are excluded from the estimation of the bone age according the recommendations to Roche *et al.*[6] and Lenko.[3]

We determined the radius-ulna-short (RUS) bone score of the Tanner-Whitehouse 2 system (TW2-RUS).[2 7] The total scores of the ratings were not analysed according to the orginal tables based on the Harpenden growth study but according to those of the more recent Zurich longitudinal growth study (TW-ZH).[10]

EQUATIONS OF PREDICTION OF ADULT HEIGHT

Tanner-Whitehouse mark I

This equation is based on three variables namely height, chronological age, and bone age (TW-ZH)[1 2 10] and, in addition, the girls are separated into premenarcheal and postmenarcheal. Taking the midparental height into account a correction factor (one third of the difference of midparental height of the subject and the midparental height of the population (midparental height Zurich=171·3 cm))[10] can be added to the prediction calculated between the bone age of 9 and 14 years and between the bone age of 7 and 13 years in boys and girls respectively

Tanner-Whitehouse mark II

This revised method replaced the Tanner-Whitehouse mark I equation described in 1975[2] and is based on samples that include tall and short children.[7] This method can be used with a minimum of three variables (chronological age, bone age, height) but additional equations are given when the height velocity or the change in bone age, or both, are known. This can improve the prediction mainly at a bone age of over 8 years in girls and 11 years in boys.[7]

Index of potential height method

This method described by Lenko and coworkers is based on the assumption that the height SD scores for bone age remains constant up to the final height.[3 11] For calculation we used the mean and SD scores of the Zurich longitudinal growth study[10] and the bone age (TW2-RUS) adapted to these norms (TW-ZH).

Bayley-Pinneau equation

This equation is based on bone age estimated by the method of Greulich and Pyle.[9] There are separate tables for normal, retarded (greater than or equal to one year) and accelerated (greater than or equal to one year) bone age. As the Swiss population seems to be retarded by six months compared with the group studied by Greulich and Pyle we used, according to the suggestion by Zachmann, the tables for retarded bone age if the bone age was retarded ≥1·5 years.[12]

Roche-Wainer-Thissen

Recumbent length is required for the Roche-Wainer-Thissen predictions.[5 6] As in our patients only the standing height was available, 1 cm was added to this value for the calculation of adult height prediction.

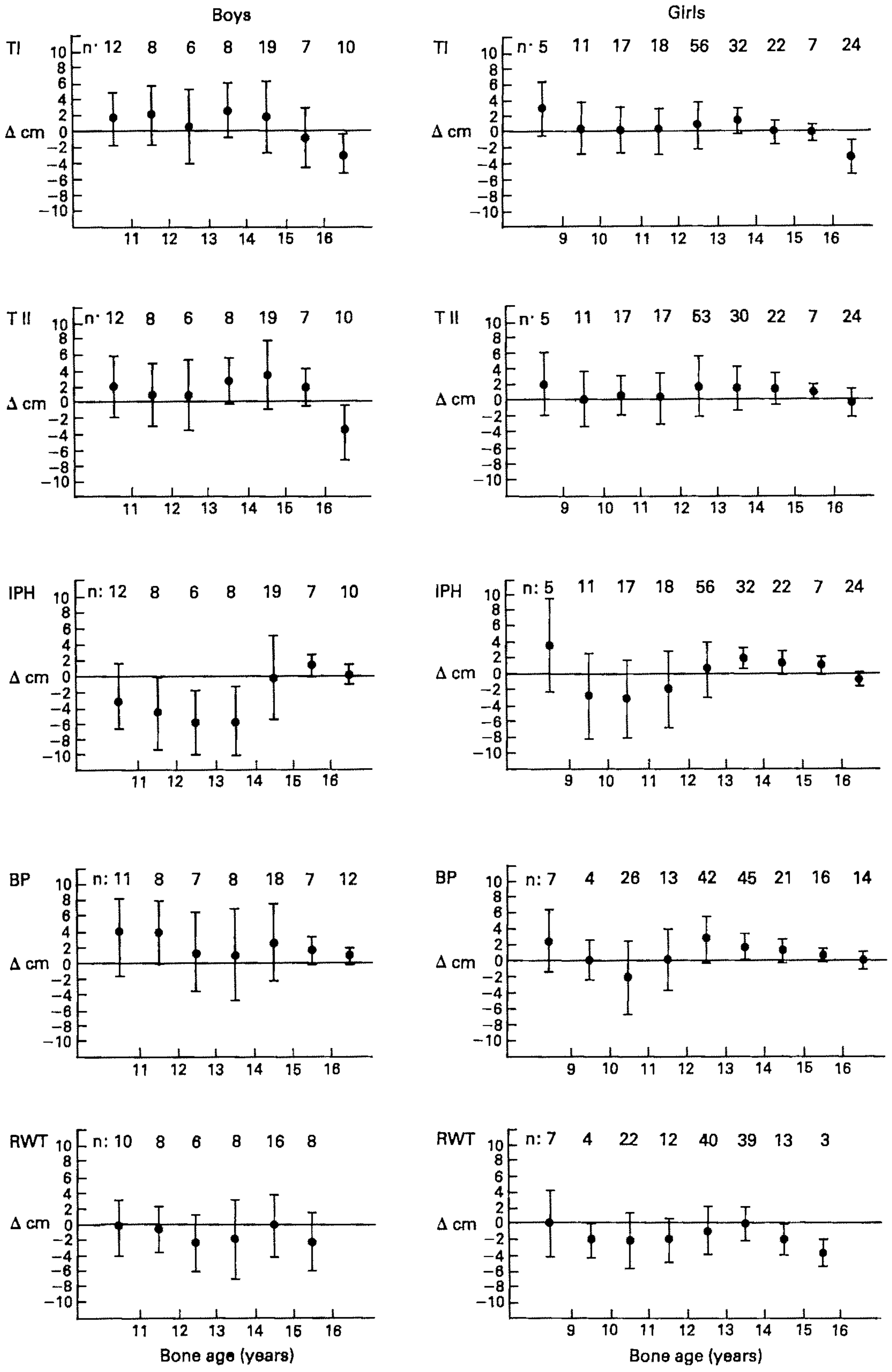
Results

Predicted adult height minus attained adult height was calculated for each of the five prediction methods. Therefore positive results indicated overestimation whereas negative results indicated underestimation of the predicted adult height by the method applied. The figure shows the mean (SD) values of these differences for each bone age year interval.

BOYS

Tanner-Whitehouse mark I equation

The Tanner-Whitehouse mark I method gave reasonably accurate results up to a bone age of 13 years but tended to slightly overestimate height for a bone age of 13–15 years. Dividing the patients with a bone age between 13 and 15 years into two groups, namely a group with a height SD score between 2 and 3 and a group with height ≥3 SD scores, it became clear that the overestimation in that age group was due to the tall boys (≥3 SD scores) and that the prediction was accurate for the boys with a height between 2 and 3 SD scores. The overestimation of final height in the very tall boys (≥3 SD scores) with a bone age of 13–14 and 14–15 years was 6·2 and 4·5 cm respectively whereas it was only 0·5 and 0·8 cm in the same bone age groups in boys with a height between 2 and 3 SD scores. In the bone age group ≥16 years the method is of no use. This is highlighted by the fact that some patients were already taller than the predicted adult height at the time of the prediction. Surprisingly the correction factor for midparental height did not improve the results; on the contrary the overestimation in the younger bone age groups was increased (data not shown).



Deviation (Δ, cm) of adult height prediction from actually achieved final height in subjects with constitutionally tall stature. Abbreviations used: T I=Tanner-Whitehouse mark 1; T II=Tanner-Whitehouse mark II; IPH=index of potential height; BP=Bayley-Pinneau; RWT=Roche-Wainer-Thissen. Overall mean (SD) values are shown. Results are presented in bone age groups. The radius, ulna, and short bones method of Tanner et al[7] *based on the data of the Zurich longitudinal growth study*[10] *bone age and the Greulich and Pyle*[9] *rating were used for the T I, T II, IPH and BP, RWT prediction methods respectively.*

Tanner-Whitehouse mark II equation

In general the same results were found as for the Tanner-Whitehouse mark I method. The Tanner-Whitehouse mark II method tended to overestimate slightly more in the bone age group 14–15 years. On 12 occasions we were able to introduce height velocity and increment of bone age as a variable in the equation. This did not improve the prediction compared with that derived from the three variables equation (data not shown). Similar to the Tanner-Whitehouse mark I method the mean overestimation in the bone age groups of 13–14 and 14–15 years was more pronounced (4·5 and 5·9 cm respectively) in the tall boys (height ≥3 SD scores) than in boys with a height between 2 and 3 SD scores (1·6 and 2·5 cm respectively). Up to the bone age of 15 years the estimated confidence limits of prediction are ±8 cm for the Tanner-Whitehouse mark I and Tanner-Whitehouse mark II estimation methods.

Index of potential height method

A marked underestimation was seen up to a bone age of 16 years. The results thereafter were accurate, however.

Bayley-Pinneau equation

This method overestimated the prediction with estimated confidence limits of prediction of ±10 cm up to the bone age of 15 years. In the older bone age groups the method was accurate with confidence limits tending to decrease.

Roche-Wainer-Thissen equation

This method gave a reasonably accurate prediction up to the bone age of 12 years followed by a slight underestimation during the bone age period of 12–14 years which gave way again to accurate prediction values for a bone age of 14–16 years.

GIRLS

Tanner-Whitehouse mark I equation

Although the method was reasonably accurate in girls with a bone age between 9 and 16 years it overestimated the adult height in the group with a bone age of less than 9 years and tended to underestimate in the group with a bone age >16 years in such a way that some girls were already taller than the predicted adult height. Notably girls who presented a bone age that was accelerated compared with their chronological age (greater than or equal to two years) showed an overestimation of adult height in the age groups 13–14 years of 3·1 cm in contrast to 1·2 cm in girls without bone age acceleration. In addition, as was seen in boys, the correction factor for midparental height made the adult height prediction even worse.

Tanner-Whitehouse mark II equation

In general the same results were found as when using the Tanner-Whitehouse mark I equation. Eighty seven predictions were performed using the additional variables (height velocity or increment of bone age, or both). A small but not significant improvement in accuracy of the prediction of adult height compared with the predictions obtained using the Tanner-Whitehouse mark I method was found (data not shown).

Index of potential height method

This method was inaccurate and of no use in the bone age groups less than 12 years. Between a bone age of 12 and 16 years a slight overestimation was found.

Bayley-Pinneau equation

The adult height was overestimated in the bone age groups less than 9 years. In the bone age group 10–11 years the overall underestimation was mainly due to the girls with an accelerated bone age of more than two years. The underestimation in these girls with an accelerated bone age was 5·0 cm in contrast to the 1·3 cm in girls with a non-accelerated bone age. There was a tendency to overestimate in the bone age groups 12–13 years. The method gave relatively accurate results thereafter.

Roche-Wainer-Thissen equation

Although this method generally underestimated the adult height it could be useful for the bone age groups less than 9 years and 12–14 years.

The estimated confidence limits for all height prediction mentioned are ±7 cm up to a bone age of 13 years and ±4 cm thereafter, presenting a tendency for improvement.

Tables 1 and 2 give the prediction method recommended for boys and girls together with the correction factors that have to be added to the calculated predicted adult height.

Discussion

Tall boys and an even larger number of tall girls are referred to paediatric endocrine clinics because information is requested regarding future growth potential. Comparison of actual and parental height, estimation of bone maturation with appropriate standards, and prediction

Table 1 Recommended height prediction method for tall boys. Mean deviations (cm) of predicted from actually achieved final height are given as correction factors to subtract or add from the calculated adult height obtained using the various prediction methods

*Prediction method**	*Bone age (years)*						
	≤11	*11–12*	*12–13*	*13–14*	*14–15*	*15–16*	*>16*
T I: all >2 SDS	—	—	0·6	2·6	1·8	—	—
T I: 2 SDS–3 SDS	—	—	—	0·5	0·8	—	—
T I: ≥3 SDS	—	—	—	6·2	4·5	—	—
T II: all >2 SDS	1·9	0·9	0·9	2·7	3·4	—	—
T II: 2 SDS–3 SDS	—	—	—	1·6	2·5	—	—
T II: ≥3 SDS	—	—	—	4·5	5·9	—	—
IPH all >2 SDS	—	—	—	—	−0·33	1·4	0·0
BP all >2 SDS	—	—	1·3	1·0	2·5	1·5	0·7
RWT all >2 SDS	−0·2	−0·5	—	—	0·2	—	—
Estimated confidence limits (2 SD) for all methods (cm)	8	8	8	8	8	2·5	1·5

*The radius, ulna, and short bones method of Tanner *et al*[7] based on data from the Zurich longitudinal growth study[10] was used for the Tanner-Whitehouse mark I, Tanner-Whitehouse mark II, and Index of potential height methods and the Greulich and Pyle[9] rating for the Bayley-Pinneau and Roche-Wainer-Thissen methods. Abbreviations: T I=Tanner-Whitehouse mark I, T II=Tanner-Whitehouse mark II; IPH=index of potential height, BP=Bayley-Pinneau, RWT=Roche-Wainer-Thissen; SDS=standard deviation score.

Table 2 Recommended prediction method for tall girls. Mean deviations (cm) of predicted from actually achieved final height are given as correction factors to subtract or add from the calculated adult height obtained using the various prediction methods

*Prediction method**	*Bone age (years)*								
	<9	*9–10*	*10–11*	*11–12*	*12–13*	*13–14*	*14–15*	*15–16*	*>16*
T I: all >2 SDS	—	0·4	0·2	0·1	0·6	1·4	−0·2	−0·3	—
T I: 2 SDS–3 SDS	—	—	−1·3	—	—	—	—	—	—
T I: ≥3 SDS	—	—	1·9	—	—	—	—	—	—
T II: all >2 SDS	—	0·2	0·5	0·2	1·8	1·4	1·4	0·9	—
IPH: all >2 SDS	—	—	—	—	0·7	1·9	1·4	1·0	—
BP: all >2 SDS	—	—	—	0·1	—	—	1·3	0·9	0·3
RWT: >2 SDS	0·0	—	—	—	−0·8	0·1	—	—	—
Estimated confidence limits (2 SD) for all methods (cm)	7	7	7	7	7	4·0	3·0	2·0	1·0

*The radius, ulna, and short bones method of Tanner *et al*[7] based on data from the Zurich longitudinal growth study[10] was used for the Tanner-Whitehouse mark I, Tanner-Whitehouse mark II, and index of potential height methods and the Greulich and Pyle[9] rating for the Bayley-Pinneau and Roche-Wainer-Thissen methods. Abbreviations. T I=Tanner-Whitehouse mark I, T II=Tanner-Whitehouse mark II, IPH=index of potential height, BP=Bayley-Pinneau, RWT=Roche-Wainer-Thissen; SDS=standard deviation score

of adult height are important tools for deciding whether or not any treatment is indicated.

Height predictions are calculated using any of the methods described here. We have to bear in mind, however, that these equations have been developed for normal children, not for children with growth disorders.[1–6] Only the height prediction method reported by Tanner and coworkers based on a large number of normal children had included samples of tall children.[7–8] Applying these methods of predicting adult height to series of tall children until ultimate adult height is reached allows a comparative evaluation of these different equations.

We analysed the validity, variability, and accuracy of the five commonly used methods of height prediction in 32 boys and 100 girls. This study clearly shows that there are different systematic errors (error between mean values of predicted height and adult height achieved) in the equations applied for predicting adult height depending on sex and on bone age at the time when the prediction was performed. It should be emphasised that there is no best or most accurate method; each method has its advantages and disadvantages under specific circumstances. Thus it is important for clinicians and investigators using height predictions to evaluate the effect of treatment to know the tendency of each method to underestimate or overestimate adult height. We suggest that the equation should be selected according to sex and actual bone age of the subject and should take into account the mean difference between predicted height and adult height achieved (systematic error) as a correction factor to add or subtract from the calculated adult height (tables 1 and 2). This procedure undoubtedly increases the accuracy of the prediction made.

Brämswig *et al* compared height predictions with ultimate adult height in boys with untreated constitutionally tall stature and found similar systematic errors by using Tanner-Whitehouse mark I, Bayley-Pinneau, and Roche-Wainer-Thissen methods of prediction of adult height.[13] In contrast Zachmann *et al* reported excellent results in predicting adult height with the Tanner-Whitehouse mark I, Bayley-Pinneau, and Roche-Wainer-Thissen methods.[14] Unfortunately boys and girls were not separately reported and therefore no direct comparison with our results is possible.[14] As adult height predictions have been rarely documented in a large number of untreated constitutionally tall girls our data have to be compared with control data derived from studies on the effect of oestrogen treatment in tall girls.[5 14–20] These data are not consistent, however. Although some workers described an overall overestimation of the adult height using the Bayley-Pinneau method[15 16 18 20] others reported accurate results applying the same method,[17 19] which only agrees with our data found for the bone age groups 12–15 years. Furthermore John and Schellong[20] and Sorgo *et al*[18] described in tall girls with a mean bone age of 13·5 years accurate height predictions using the Tanner-Whitehouse mark I method and we found an overestimation for exactly that age group. In addition Zachmann *et al* found an improvement in the accuracy of the Tanner-Whitehouse mark I method when the correction factor for midparental height was added.[14] In contrast our results and those of Sorgo *et al*[18] did not support the conclusion that a correction factor for midparental height improved the accuracy of the predictions of adult height.

It is of importance to note that all prediction methods used in our study had in addition to a systematic error a large relative error (SD of mean values of the prediction method used) in predicting adult height up to a bone age of 13 years in girls and 15 years in boys. In other words an accurate prediction is not possible until the peak height velocity has passed. There are two main reasons for this observation, which not only occurs in tall but also in normal children and children with short stature. First, the bone age, the basic variable of any prediction method, is not a well defined measurement and is dependent on human assessment.[21 22] Like any other measurement, the bone age rating is subject to an interobserver (comparability) and an intraobserver (replicability) error.[22] The smallest differences in the bone age rating therefore result in a considerable difference in adult height prediction when methods that rely heavily on the bone age rating, such as the Bayley-Pinneau[4] and index of potential height methods[3 11] are used. Furthermore using the Greulich and Pyle atlas it is noteworthy that for girls the radiographs depicting the age standard

11 and 12 years are similar.[9] Second, puberty and its growth spurt are dynamic processes that are not consistent. In addition the height gain during the pubertal growth spurt is variable and by no means concordant with the bone age advancement. Thus in consulting with patients the large confidence limits of the predictions must be discussed and it is wise not to give an exact value for the adult height to be achieved but rather the possible range of prediction.

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Incidence of hepatic hamartomas in tuberous sclerosis

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Abstract

Hepatic hamartomas were thought to be a rare finding in patients with tuberous sclerosis. The purpose of this study was to assess their incidence in children with tuberous sclerosis and to review the literature.

During 1984–90 we examined 51 children by ultrasonography; there were 25 boys and 26 girls. Their age ranged from 3 months to 18 years. Liver hamartomas were seen in 12 (23·5%) of the children, more often in girls than boys (5:1). Their incidence increased with age reaching 45% in children over the age of 10. They did not produce any symptoms of hepatic dysfunction.

Our study and review of reported cases prove that hepatic hamartomas are a common finding in patients with tuberous sclerosis and may be very helpful in providing a more accurate diagnosis and consequently help in genetic counselling.

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Tuberous sclerosis is a genetic disorder with multiple hamartomas, autosomal dominant inheritance, variable expressivity, and high penetrance. Its expression may vary greatly with some individuals showing no clinical signs of the disorder and others manifesting severe seizure disorders, mental retardation, and involvement of multiorgan systems including skin, brain, heart, kidneys, retina, and liver.

The most common visceral lesions are renal angiomyolipomas, which have been studied extensively by others and are found in 52–89% of patients.[1 2]

Hamartomas of the liver in association with tuberous sclerosis are usually found incidentally on postmortem examination,[3 4] with selective angiography,[5–7] computed tomography,[8 9] or by ultrasonography.[10–12] The incidence of hepatic lesions, however, has been evaluated in only one large study.[12]

Table 1 Ultrasonographic findings in 12 children and three parents with liver hamartomas associated with tuberous sclerosis

Case No	*Age (years)*	*Sex*	*Liver lesion*	*Associated kidney lesion*
1	12	F	Multiple, largest 0·7 cm	AML
2	12	F	Multiple, 0·5–0·7 cm, calcification, right lobe	AML
3	10	F	Single, calcification, right lobe	AML, cysts
4	1·5	M	Single, 0·6 cm, left lobe	None
5	8	F	Multiple, 0·5–0·7 cm	None
6	13	F	Multiple, largest 0·7 cm	AML
7	5	F	Multiple, 0·5 cm	None
8	9	F	Multiple, 0·5–0·8 cm	AML, clear cell sarcoma
9	0·7	F	Multiple, 0·5 cm	AML
10	6	M	Single, 0·7 cm, right lobe	AML
11	8	F	Multiple, 0·5–0·7 cm	AML, cysts
12	13	F	Multiple, largest 0·8 cm	AML
13	35	F	Multiple, largest 2·5 cm	AML
14	22	F	Single, 0·7 cm, right lobe	AML
15	41	M	Multiple, 0·5–0·8 cm	None

AML=angiomyolipoma

We evaluated the incidence of hepatic hamartomas in children with tuberous sclerosis and reviewed the literature on previously reported cases.

Patients and methods

During the period 1984–90 we examined 51 children by ultrasonography; there were 25 boys and 26 girls. The age of patients ranged from 3 months to 18 years (mean age 6·8 years). There were 20 patients under 5 years of age, 20 children between 5 and 10 years, and 11 patients over the age of 10.

The diagnosis of tuberous sclerosis was established in all patients by careful history taking and examination of the skin, nails, hair, and eyes according to the Gomez criteria for tuberous sclerosis.[13] Cerebral computed tomography and ultrasonography of the heart were also done.

Ultrasonographic examinations of the upper abdomen were performed with a sector scanner, using a 3·75 or 5 MHz transducer to evaluate the liver, kidneys, pancreas, and spleen. Four parents with tuberous sclerosis were examined by the same method.

Results

Hepatic hamartomas were seen in 12 (23·5%) of the 51 examined children. They were found more often in girls than boys (5:1) and their incidence increased with age.

Areas of increased echogenicity compared with the surrounding hepatic parenchyma were found in two out of the 20 children (10%) below the age of 5 years (an 8 month old girl and a 1·5 year old boy), in five out of the 20 children (25%) between 5 and 10 years, and in five out of the 11 patients (45%) over the age of 10. Usually, the hamartomas were multiple (n=9) and localised in both liver lobes. They all measured from 0·5 to 0·8 cm in size. Calcification in these lesions was found in two girls aged 10 and 12 years (table 1).

In nine out of 12 children with liver involvement ultrasonography also revealed multiple bilateral angiomyolipomas of the kidneys. In two of these children renal angiomyolipomas coexisted with cysts and in one 9 year old girl, renal angiomyolipomas coexisted with a clear cell sarcoma. After several years of good health, during which this girl did not come for follow up examination, she developed a relapsing fever. Except for the hepatic hamartoma, ultrasound study of the kidneys showed a large tumour of 6×6×9 cm in the right kidney and bilateral, multiple angiomyolipomas. She underwent radical nephrectomy but died three months after surgical intervention.

In none of the children, with the exception of the girl with renal clear cell sarcoma, did we observe any clinical symptoms or signs of hepatic or renal dysfunction. The blood pressure and all biochemical tests including concentrations of electrolytes, serum creatinine, and uric acid and activities of alkaline phosphatase, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase were within normal limits. There was no blood or protein in the urine.

Hepatic hamartomas were seen in three out of four parents with tuberous sclerosis: two women and one man. Both women, 22 and 35 years of age, demonstrated hepatic hamartomas coexisting with multiple renal angiomyolipomas. Similar changes, both hepatic and renal, were revealed in their daughters, 8 months and 12 years of age, respectively. Ultrasonographic examination of the 41 year old man showed multiple hepatic hamartomas and a normal picture of both kidneys.

Discussion

For many years hepatic hamartomas were regarded as an unusual finding in tuberous sclerosis. However, we have found 28 patients with tuberous sclerosis and liver involvement in the medical literature (table 2).

The incidence of hepatic lesions has been evaluated only in two reports.[6 12] Compton *et al* demonstrated vascular tumours of the liver with coeliac angiography in five out of eight patients; their ages were 10 months (two patients), 11·2 and 29 years.[5] In the study of Fleury *et al* hepatic hamartomas were revealed by ultrasonography in 13% of patients (three out of 23) under 16 years of age and in 23% (three out of 13) in the other patients.[12]

Our results prove that the incidence of hepatic hamartomas may be even higher, reaching 45% in children above 10 years of age.

In the reviewed literature hepatic hamartomas were found more often in females than males, with the ratio 19:9. In our study this predominance was even more apparent (5:1).

Hepatic hamartomas in tuberous sclerosis seem to be benign and asymptomatic. In contrast to renal lesions, hepatic hamartomas were not mentioned as a possible cause of death in patients with tuberous sclerosis in a large study of 355 patients at the Mayo Clinic.[21]

None of the children examined in our study had any manifestation of hepatic dysfunction. In the literature we could not find any description of hepatic manifestations in tuberous sclerosis patients with liver involvement except for one patient presented by Kristel and Sperber.[20] These authors described a 10 year old girl with tuberous sclerosis who was examined after blunt abdominal trauma. Computed tomography and ultrasound showed a hepatic tumour in the left lobe, which enlarged during the next several months and forced them to carry out a hepatic lobectomy.

Histopathological examination of hepatic hamartoma was available in several cases. Hepatic angiomyolipomas were the most common tumours found in patients with tuberous sclerosis.[10 16 18 20] The other reports also mentioned neurilemmoblastoma,[14] lipomesenchymal tumour,[15] hamartoma,[3] and lipoma.[17]

Interestingly, haemangioma, the most common benign tumour of the liver was not seen in any of histopathologically examined patients with tuberous sclerosis.

Diagnosis of vascular hepatic tumours in tuberous sclerosis was suggested in several reports in angiographic[6–8] and ultrasonographic studies.[12] We suppose that angiographic findings in the liver of patients with tuberous sclerosis may resemble vascular expression of angiomyolipomas more than real haemangioma. Unfortunately, computed tomography of the liver was not performed in any of the aforementioned studies.

The ultrasonographic appearance of lipomatous masses cannot be easily differentiated from haemangioma. The pattern is not specific for angiomyolipomas, therefore, ultrasound studies should be supplemented by computed tomography. Contrast enhanced computed tomography is able to provide greater detail by demonstrating low density areas that represent fatty tissue.

We believe that the diagnosis of hepatic angiomyolipomas in our patients is highly probable. But as none of them presented symptoms of hepatic dysfunction, and, as patients with liver hamartomas in tuberous sclerosis seem to have a good prognosis, we decided not to perform computed tomography as a routine procedure. Ultrasonographic assessment of the liver should be performed together with kidney evaluation in follow up studies.

Roberts *et al* stressed a relationship between renal angiomyolipomas and hepatic tumours in patients with tuberous sclerosis.[19] Their study of a group of 50 patients with renal angiomyo-

Table 2 Hepatic hamartoma: review of the literature (total 28: 19F/9M)

Authors (in chronological order)	*No of patients*	*Sex*	*Age (years)*	*Diagnosis of liver lesions*
Inglis[14]	1	F	41	Neurilemmoblastomas
Cares[15]	1	F	25	Lipomesenchymal tumours
Perou and Gray[16]	1	F	23	AML, polycystic lesions
Viamonte *et al*[3]	1	F	25	Hamartoma
Ramchand *et al*[17]	1	M	24	Lipoma
Chonko *et al*[5]	1	F	22	Vascular abnormalities
Compton *et al*[6]	5	F	11	Hamartoma
		F	10/12	Hamartoma
		M	29	Hamartoma
		F	24	Hamartoma
		F	10/12	Hamartoma
Kagan and Steckel[10]	1	M	1[illegible]	AML
Grasso *et al*[4]	1	M	[illegible]/12	Atypical, large hepatocytes
Newmark *et al*[8]	1	F	52	AML
Marsidi and Wise[7]	1	F	23	Precapillary angiomas
Ilgren and Westmoreland[11]	1	F	2[illegible]	AML
Rosen *et al*[9]	1	M	2[illegible]	Fatty lesion, AML?
Roberts *et al*[19]	3	M	26	Lipomatous tumors, AML?
		F	25	Lipomatous tumors, AML?
		F	42	Lipomatous tumors, AML?
Fleury *et al*[12]	6	2M/4F	6–48	Harmartomas. Haemangiomas?
Kristal and Sperber[20]	1	F	10	AML
Green *et al*[11]	1	M	40	Fibromas

AML-angiomyolipoma

lipomas revealed lipomatous tumours of the liver in five patients. Three of them were known to be affected with tuberous sclerosis.

Renal angiomyolipomas were found in 85% (24/28) of tuberous sclerosis patients with liver involvement reported in the literature and in 75% (9/12) of children in the presented study. However, these figures cannot prove that any relationship between renal and hepatic angiomyolipomas exists. In our experience renal angiomyolipomas appear before hepatic hamartomas and both develop with age. This evolution of the lesions may result in their frequent coexistence in older children and adults.

We conclude that liver hamartomas are a very valuable feature in the diagnosis of tuberous sclerosis, especially of formes frustes. In the absence of long term studies, periodic monitoring with hepatic and renal ultrasonography is recommended for all patients with tuberous sclerosis.

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Increased resting energy expenditure in childhood asthma: does this contribute towards growth failure?

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Abstract

In order to determine whether or not there was a relationship between disorders of growth in children suffering from asthma and either increased resting energy expenditure or inadequate energy intake, a group of 34 children suffering from perennial symptoms were studied. A control group matched with the asthmatic children for sex and fat free mass were similarly studied.

The children kept seven day records of weighed food intake. Basal metabolic rate was measured on one occasion in the fasted state by means of indirect calorimetry using the ventilated hood technique. The asthmatic children kept a 28 day record of peak expiratory flow rates, asthma symptoms, and medication usage.

The asthmatic children expended significantly more energy at rest than their matched controls in absolute terms (14%). There was no correlation between height or height SD score and any parameter of energy balance. The causes of these finding are as yet speculative.

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The interaction of the disease process, drug treatment, and energy expenditure and their effect on growth in chronic disease states, such as asthma, are poorly understood. While an association between asthma and short stature is well recognised,[1 2] the factors that contribute towards poor growth and the incidence of the problem are less well documented.[3 4]

Since Cohen *et al* first described growth disorders in asthmatic children in 1940[1] attempts to quantify and explain the problem have been confounded by a number of obstacles. The definition of asthma and hence its incidence has changed considerably over the last 20 years.[5] The term 'asthma' now encompasses a much broader spectrum of disease.[6 7]

Growth is the end result of a number of physiological pathways. Simplistically a reduction in the rate of growth is a consequence of an imbalance between energy intake and energy expenditure. Three factors must be considered: dietary intake, abnormal excretory losses, and the nature and magnitude of metabolic demands. Such imbalances may be small and accrue over prolonged periods of ill health or result from repeated periods of acute exacerbations of disease. Deficiencies of specific micronutrients that may also limit growth once energy needs are satisfied should not be overlooked.[8] There have been no studies in which both intake and expenditure of energy have been determined in children with asthma.

The purpose of this study was to examine the extent to which poor growth in asthmatic children could be attributed to poor energy intake or an increased metabolic demand for energy. Measurements of energy intake and basal metabolic rate (BMR) were made for children suffering from chronic perennial asthma of comparable severity between acute exacerbations of their asthma. Their results were compared with those from normal healthy children matched for sex and fat free mass.

Patients and methods

This study was conducted with the approval of the Southampton and South West Hampshire Health Authority ethical committee and informed consent was obtained from the parents of all of the children that took part.

Thirty four children (25 boys, nine girls) aged 6·8–12·7 years (mean 8·6 years) suffering from chronic perennial asthma were recruited from the paediatric outpatient clinic at Southampton General Hospital. All of the children were graded as Tanner score 1 for sexual maturity on physical examination.[9] Each of the asthmatic children kept a diary in which they recorded their use of medication and measurements of peak flow for a period of 28 days. Peak expiratory flow rate (PEFR) was determined as the best of three attempts at peak flow measurements on rising in the morning before administration of inhaled bronchodilators and again before retiring. From this the number of days when the PEFR was less than 75% of the predicted value for that child and the days when the diurnal variation exceeded 25% of the predicted PEFR were calculated. Thirty four healthy prepubertal children recruited from local schools were matched with the study children for sex and fat free mass. None of the control group suffered from asthma. The control subjects were aged 5·39-11·78 years (mean 8·67 years).

Weighed dietary intake was recorded for a period of seven days in the standard manner described by Marr,[10] using digital electronic scales (Hanson). The children and their families were instructed in the use of the scales and how to record their food and drink consumption in a notebook provided. The dietary record was checked during a follow up interview with the dietitian. These were then coded according to the McCance and Widdowson food tables.[11] Using a computerised database (Microdiet), analysis was carried out to determine the estimated metabolisable energy intake over the seven day period. Energy intakes were expressed in absolute units, corrected for differences in fat free mass, and in relation to that recommended by the Department of Health and Social Security.[12]

In this study, energy expenditure at rest or BMR was defined as the minimum energy expenditure for maintaining essential bodily functions under standardised resting conditions, 12–18 hours postprandial. All measurements were performed between 0730 and 1030, after an overnight fast. BMR was determined by indirect calorimetry using an open circuit ventilated hood system. Oxygen consumption and respiratory exchange ratio were measured to calculate BMR.[13] During the measurement the subjects lay supine on a bed listening to music or story tapes. Room temperature was maintained at 22–24°C. The measurements were conducted for a minimum period of 30 minutes after a stable energy expenditure was achieved.

All of the asthmatic children received inhaled bronchodilator on the morning of the study via the route and in the dose to which they were accustomed. Those normally taking inhaled steroids took their usual dose. None of the children were taking oral theophylline. All of the asthmatics were subjectively well on the day of calorimetry.

BMR was expressed in kJ per 24 hours, corrected for differences in fat free mass, and as a percentage of that predicted on the basis of age, gender, weight, and height.[14]

Table 1 PEFR and steroid dose in asthmatic children (n=34)

	No steroids (n=10)	*Steroids (n=24)*
PEFR <75% predicted value (days/28 days)	15 (0–28)	2 (0–25)
Morning dip in PEFR >25% of predicted value (days/28 days)	0 (0–2)	0 (0–4)
Steroid dose (µg/day beclomethasone dipropionate)	—	400 (100–200)

Height was determined using a Holtain stadiometer and the height SD score[15] and the predicted height allowing for mean parental height were determined.[16] Weight was determined by standing balance scales. Fat free mass was determined from skinfold thickness (biceps, triceps, subscapular, and suprailiac sites) measured using Harpenden skinfold callipers and used to determine body density, body fat, and fat free mass.[17 18]

The results were analysed using non-parametric statistics. Values given are median and ranges. Differences between the asthmatic children and their matched controls were analysed using the Wilcoxon matched pairs test. Differences within the asthmatic group were analysed with the Mann-Whitney test.

Results

Of the 34 asthmatic children who entered the trial, 24 were taking regular inhaled beclomethasone dipropionate for at least three months. The mean (SD) dose of steroid was 341·8 (322·0) µg/24 hours. Only one child was receiving regular oral steroids (prednisolone 2·5 mg on alternate days). All of the children took inhaled salbutamol. None of them was taking oral theophylline.

There was no significant difference in the number of days on which the children were assessed as having appreciable reduction in PEFR between the children on inhaled steroids and those that were not (see table 1).

The anthropomorphic characteristics of the asthmatics and the controls are shown in table 2. There was no statistically significant differences between the asthmatics and controls in age, although the asthmatic children were significantly shorter (p<0·05), were lighter

Table 2 Characteristics of asthmatic and control children, values are median (range)

	Controls (n=34)	*Total asthmatics (n=34)*	*Asthmatics*	
			No steroids (n=10)	*Steroids (n=24)*
Age (years)	8·5 (5·4–11·8)	8·3 (6·7–12·7)	8·9 (6·8–10·8)	8·1 (6·7–12·7)
Weight (kg)	27·5 (20·5–39·0)	26·0 (17·5–38·4)**	27·7 (22·0–36·4)	24·3 (17·5–38·4)
Height (cm)	132·0 (110·0–147·7)	127·0 (110·0–153·0)*	131·0 (123·0–153·0)	125·2 (110·8–140·7)†
Height SD score	0·38 (−1·52 to 2·13)	−0·47 (−2·05 to 2·33)	0·26 (−0·10 to 1·04)	−0·67 (−2·00 to 2·30)
% Body fat	17·0 (6·6–32·9)	12·7 (6·3–28·2)**	13·6 (10·2–24·5)	10·7 (6·3–28·3)
Fat free mass (kg)	23·0 (17·3–31·7)	23·0 (17·4–31·0)	23·9 (19·1–31·0)	22·3 (17·4–28·2)

*p<0·05, **p<0·01, significantly different from controls, †p<0·05, significantly different from no steroids.

Table 3 Energy intake and BMR of asthmatic and control children, values are median (range)

	Controls (n=34)	*Total asthmatics (n=34)*	*Asthmatics*	
			No steroids (n=10)	*Steroids (n=24)*
Engery intake:				
MJ/day	7·41 (5·19–11·22)	8·28 (4·27–14·88)	8·25 (5·91–10·00)	8·29 (4·27–14·88)
kJ/kg fat free mass/day	340 (224–415)	352 (188–541)	328 (253–523)	368 (188–541)
Intake BMR ratio	1·62 (1·10–2·60)	1·60 (0·90–2·40)	1·60 (1·15–1·90)	1·60 (0·91–2·40)
BMR:				
MJ/day	4·56 (3·48–6·07)	5·21 (3·50–6·36)**	5·26 (4·76–6·14)	4·86 (3·50–6·36)
kJ/kg fat free mass/day	206 (130–266)	221 (186–279)**	218 (186–277)	225 (188–279)
%Predicted BMR	104 (65–126)	110 (70–127)**	110 (100–130)	110 (70–130)

*p<0·05, **p<0·01, significantly different from controls

($p<0.01$) and exhibited a lower percentage body fat ($p<0.01$).

The mean BMR of the asthmatic group was significantly greater than controls when expressed in absolute units (14%, $p<0.01$), relative to fat free mass (11%, $p<0.01$) or as a percentage of the BMR predicted[14] from age, sex, and weight (11%, $p<0.01$; see table 3).

Although there was a trend to higher energy intakes both in absolute terms and per kg fat free mass, this difference did not attain statistical significance.

The mean (SD) energy intake expressed as a ratio of BMR was 1·65 (0·34) and 1·68 (0·37) for the asthmatic and control groups respectively. Further analysis revealed that these results were not influenced by steroid usage.

Six of the asthmatic children were noted to have eczema at the time of the study. These children were found to be either less than the 25th centile for height or growing at a height growth velocity of less than the 25th centile for the year before entry into the study. None of the control children had eczema or a history of the disorder.

Discussion

Over the last 30 years many authors have suggested a link between poor growth and childhood asthma.[1–4] [19] [20] Such a link is an appealing concept as many of the chronic diseases of childhood are associated with short stature.[21] In the asthmatic child however it is not easy to postulate a mechanism for this association. The use of steroids has not been uniformly incriminated.[22] [23] There is no evidence of chronic malabsorption in the majority of children and the possibility of a fundamental disorder of growth has not been substantiated.

A distinctive pattern of height growth has however been described.[4] [20] Asthmatic children appear to grow at a slightly slower rate initially. They fail to experience the acceleration in growth velocity at the same time as their non-asthmatic peers and they have delayed bone ages. Their adolescent growth spurt tends to be delayed as does the onset of sexual maturation but most children will eventually attain their predicted adult height.

One study that explored the possibility of dietary inadequacy in asthma failed to show a reduced energy intake in short asthmatics and energy supplementation failed to improve their rate of growth.[24] The role of energy loss in allergic disease is as yet only partially understood.

Increased energy expenditure may occur during attacks of asthma when there is a dramatic increase in the energy cost of breathing.[25] [26] If medication such as inhaled steroids reduced the frequency of exacerbations, it is reasonable to postulate that this might have a benefical effect on overall energy expenditure. The superimposed effects of steroids on linear growth makes this a rather difficult hypothesis to test.

This study represents the first occasion in which energy intakes and basal metabolic rates have been determined in children with chronic asthma. The results suggest that the asthmatic children receiving conventional inhaled treatment have a slightly greater metabolic demand for energy at rest. The raised BMR may be attributable to one or more of several factors. The metabolic demand for energy may be increased by the inflammatory response associated with asthma.[27] It is noteworthy that eight of the smallest children had mild eczema. The degree of eczema was unlikely to cause significant protein or fluid loss but might represent a further increase in inflammatory response with a potential increase in metabolic rate. Little information is as yet available about the effect of skin disease on BMR. Food allergies and consequent malabsorption in asthmatics does not appear to be a clinically significant problem in most children. Energy used in the work of breathing may be increased.[4] Finally, the medication used in an attempt to control the disease may result in alterations in energy expenditure. Vaisman and coworkers have shown that after a single dose of salbutamol a variety of systemic effects may be evident for periods of 3–4 hours.[28] Energy expenditure at rest increased by 10% over the first hour after salbutamol inhalation and remained raised for up to 90 minutes. They suggest that such drug related changes in energy expenditure may be important in patients receiving long term bronchodilator treatment. This drug related effect would however account for only a small proportion of the increase in BMR observed in this study.

The increase in BMR in the asthma group was associated with a comparable increase in energy intake of approximately 11%, such that the energy intake:BMR ratios were of the same magnitude. This observation would add further support to the view that the metabolic demand for energy was increased in chronic asthma. It was not possible to demonstrate a relationship between elevated BMR, or low energy intake: BMR ratios and the magnitude of a growth deficit. A single estimate of growth and energy balance using the approaches adopted in this study would be unlikely to be sufficiently sensitive to detect such a direct causal relationship. Furthermore, any increases in BMR may well be compensated for by reductions in the energy expended in physical activity. Expansion of this study to determine long term energy expenditure would help to ellucidate the relationship between expenditure and intake. Recently refined techniques allowing determination of BMR during exercise might add very useful information to the understanding of energy utilisation during activity in asthmatic children. Even if the energy cost of activity were increased, a reduction in the amount of physical activity through breathlessness or anxiety would reduce the amount of energy expended in physical activity.

The results of this study do suggest, however, that the disease process and long term bronchodilator treatment may adversely affect energy balance in patients with chronic lung disease such as asthma. Further studies are required to further explore the extent to which alterations in energy expenditure may contribute towards poor growth in children with asthma.

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Defective alloantigen-presenting capacity of 'Langerhans cell histiocytosis cells'

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Abstract

The functional activity of skin cells derived from an infant who died of multisystem Langerhans cell histiocytosis (LCH) was examined. Involved and non-involved skin was obtained at postmortem examination within three hours of death; normal epidermal Langerhans cells and 'LCH cells' were separated by means of dispase digestion. The functional activity of different populations of CD1a positive cells was assessed using the conventional six day allogeneic mixed cell reaction. Compared with Langerhans cells from a healthy control, LCH cells showed minimal functional activity. However, Langerhans cells from non-involved skin showed normal and Langerhans cells overlying involved skin showed augmented functional activity. These findings suggest that LCH is a disease in which abnormal Langerhans cells accumulate and/or proliferate in various tissues but it does not affect the entire Langerhans cell population.

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Langerhans cell histiocytosis (LCH), a rare disorder of unknown cause affecting both children and adults, can involve many different organs and present to a wide range of medical specialties. LCH is now regarded as a 'reactive' disorder in which cells bearing the Langerhans cell phenotype accumulate and/or proliferate in physiologically normal and abnormal sites.[1,2] The subsequent local tissue damage may cause organ dysfunction and in severe cases, death. The tissue destruction in LCH is believed to be at least partly the result of excess cytokine production.[3] Although lesional 'LCH cells' express most of the phenotypic markers as epidermal Langerhans cells[4] including HLA-DR and the CD1a complex, it is not known whether these cells carry the functional capacity of Langerhans cells. Functional studies have been severely hampered by the scarcity of fresh pathological specimens.

Case report

An 8 month old boy presented with a skin rash, discharging right ear, and easy bruising from the age of 3 months. Moderate hepatosplenomegaly was evident. Investigations showed anaemia (haemoglobin concentration 65 g/l) and thrombocytopenia (platelet count $3{\cdot}0 \times 10^9$/l). A skin biopsy specimen and bone marrow aspirate both demonstrated patchy infiltration by large cells with cleaved nuclei which showed positive immunostainings to S100 and peanut agglutinin. A diagnosis of multisystem LCH was made according to the criteria of the Histiocyte Society.[5]

The child's illness progressed over the next nine months with pancytopenia requiring frequent transfusions and worsening hepatosplenomegaly. Several systemic agents including high dose systemic prednisolone, etoposide, vinblastine, and cyclosporin were tried with only transient benefit. From October 1990 he developed persistent unexplained abdominal pain, distension, and diarrhoea and in February 1991 he died of progressive disease. Postmortem examination carried out within three hours of death showed involvement of the bone marrow, lungs, skin, gastrointestinal tract, pancreas, liver, and spleen by LCH.

In order to assess the functional activity of LCH cells, samples of clinically normal skin and skin affected by LCH were taken. Small samples were snap frozen for immunohistochemistry using anti-CD1a monoclonal antibodies (MAbs) to identify the presence and localisation of Langerhans cells and LCH cells. Skin obtained from an adult patient who underwent abdominoplasty provided control epidermal Langerhans cells.

ASSESSMENT OF LCH AND LANGERHANS CELL FUNCTION

An allogeneic mixed cell reaction was used to assess the functional activity of Langerhans cells and LCH cells. Ninety six well, round bottomed microtitre plates were used in a conventional six day assay. 'Stimulator cells' were prepared from both patient and control skin. The epidermis was separated using dispase (2 mg/ml) and a single cell suspension prepared by trypsinisation (trypsin 0·05% and EDTA 0·02%). Dermal cells were isolated by collagenase digestion (0·5 mg/ml). Cells were resuspended in Roswell Park Memorial Institute medium containing 10% heat inactivated normal human serum with epidermal cells at 3×10^6 ml and dermal cells at 10^6 ml and irradiated with 3000 cGy. Aliquots of 100 μl of doubling dilutions of these cells were used per well in the functional assay. The four different stimulator cell populations were analysed using MAbs against CD1a and HLA-DR with a standard indirect immunofluorescence technique.

Peripheral blood mononuclear cells (PBMC) separated from venous blood from three healthy volunteers were used as the 'responder cells' at 3×10^5 well.

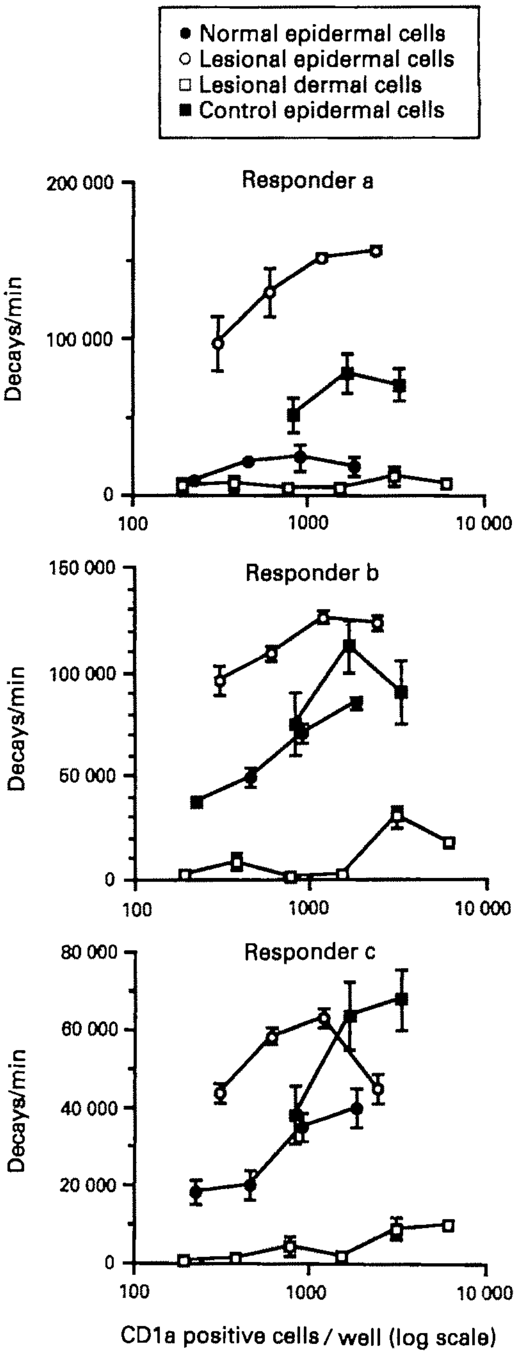
Results

PHENOTYPIC ANALYSIS

Non-involved skin showed a dense dermal infiltrate with rounded, CD1a-positive LCH cells but with no epidermal invasion. Epidermal Langerhans cells, which could be differentiated from LCH cells microscopically by their dendritic nature, were identified in epidermis at normal densities. Analysis of the stimulator cell populations is shown in the table.

Stimulator cells bearing CD1a and HLA-DR antigens as demonstrated by indirect immunofluorescence technique

	CD1a	*HLA-DR*	*Viability*
Patient's normal epidermal cells (%)	1	1	90
Patient's lesional epidermal cells (%)	1	1	90
Patient's lesional dermal cells (%)	40	41	90
Normal control epidermal cells (%)	1	1	85



Alloantigen-presenting activity of various stimulator cell populations: patient's normal epidermal cells, patient's lesional epidermal cells, patient's lesional dermal cells, and normal control adult epidermal cells, to three responder populations (a, b, and c) in a six day mixed cell reaction. The results are expressed as the mean (SEM) of $[^3H]$-thymidine incorporation in decays/min which have been corrected for baseline radioactivity in the negative controls.

FUNCTIONAL ACTIVITY OF CELL POPULATIONS (FIGURE)

CD1a positive cells in lesional dermis demonstrated minimal functional activity on a per cell basis to the PBMC of all three responders. Langerhans cells from the non-involved epidermis showed similar dose related functional activity to Langerhans cells from the control skin. Langerhans cells from the epidermis overlying the involved dermis demonstrated an exaggerated functional activity against all three responder cell populations.

Discussion

Langerhans cells represent a well defined bone marrow derived cell population in the human epidermis. They constitutively express CD1a and HLA-DR[6 7] and have a vital role as antigen-presenting cells in the skin.[8] LCH is a reactive disorder in which cells bearing the Langerhans cell phenotype accumulate and/or proliferate in physiologically normal and abnormal sites. The subsequent local tissue damage may cause organ dysfunction and in severe cases, death. The in vitro functional capacity of LCH cells as antigen presenting cells has not so far been examined.

In the present study we use the allogeneic mixed cell reaction to assess the functional activity of LCH cells; this assay has been used extensively as an investigative tool for dissecting the functional activities of antigen-presenting cells. Antigen-presenting cells are believed to provide unique stimulatory signals to resting T cells in primary allogeneic mixed cell response.[9–11] In vitro allogeneic mixed cell reaction is believed to represent the sensitisation and effector phases of graft rejection in vivo.[12]

In this study we have demonstrated for the first time that, compared with normal Langerhans cells, lesional LCH cells from a patient with multisystem LCH are unable to present alloantigens to naive T cells in vitro. Although LCH cells share the same phenotype as Langerhans cells, they show defective functional activity. This discrepancy was not due to the different ways in which the epidermal and dermal cells were treated as we found that collagenase treatment does not significantly affect the function of normal Langerhans cells (unpublished data).

The Langerhans cells in normal skin from our patient showed normal functional activity. This finding suggests that the defective functional characteristic of LCH cells is localised to these cells and does not involve the entire Langerhans cell population. The significance of the increased functional activity of Langerhans cells overlying the involved dermal infiltrate is unclear but it is possible that cytokines generated in the underlying dermal infiltrate activate the overlying Langerhans cells.

The profound restrictions on work in this disease due to the difficulties in obtaining fresh viable tissues make this study unique. Further studies will concentrate on purifying LCH cells in order that the present results can be validated. The results of this study do, however, strongly suggest that LCH is a disease in which functionally abnormal Langerhans cells accumulate and/or proliferate in various tissues but the abnormality seems to be confined to the lesional LCH cells.

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Interleukin-2 in relation to T cell subpopulations in rheumatic heart disease

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Abstract

Interleukin-2 (IL-2) and T cell subpopulations were evaluated in children with rheumatic heart disease (RHD). Three groups were included: 13 patients with active RHD, 12 with non-active RHD, and 14 control children. Serum IL-2 and T cell subpopulations were measured by radioimmunoassay and monoclonal antibodies respectively.

Patients with active RHD showed a significant increase in IL-2 concentrations and helper:suppressor (H:S) ratio compared with controls with a mean (SEM) IL-2 of 3·48 (0·62) *v* 1·26 (0·16) U/ml and H:S ratio 2·31 (0·14) *v* 1·66 (0·04). There was a significant decrease in T suppressor (CD8+) and pan T (CD3+) cells compared with controls with a mean (SEM) for CD8+ of 23·75 (1·19) *v* 32·23 (0·56)% and CD3+ of 79·55 (0·94) *v* 85·00 (0·11)%.

Patients with non-active RHD showed a significant decrease only in the CD3+ cells (78·20 (0·20)%) when compared with controls. A deficiency of CD3+ cells is a constant finding in patients with RHD, whether the disease is active or not.

There was a significant increase in IL-2 concentration with a significant decrease in CD8+ cells in patients with active RHD in comparison with the non-active group (mean (SEM) IL-2 of 3·48 (0·62) *v* 1·85 (0·24) U/ml and CD8+ of 23·75 (1·19) *v* 28·83 (1·91)%). Thus an increase in IL-2 and a decrease in CD8+ cells may be related to rheumatic activity. T helper (CD4+) cells did not differ significantly between groups.

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Interleukin-2 (IL-2) is a major lymphokine secreted by T cells after their stimulation with a mitogen or allergen.[1] One of the cellular events of immune reaction is secretion of IL-2. This IL-2 activates killer cells and supports growth of T and B cells via binding to specific surface receptors. Altered immune response to streptococcal antigens is implicated in the pathogenesis of rheumatic fever and rheumatic heart disease (RHD).[2] This altered immune response was mentioned as a diminished blastogenesis, increased leucocyte migration inhibition, and increased natural killer cell cytotoxicity.[3 4] Because of the importance of cytokines in the events of the immune reaction in various rheumatic diseases, we studied serum concentrations of IL-2 and T cell subpopulations in patients with active and non-active RHD.

Patients and methods

Three groups of children were studied. (1) Thirteen patients had active RHD and all met the revised Duckett-Jones criteria for diagnosis of active rheumatic fever.[5] They were aged 8–12 years (mean (SE) 9·2 (0·1) years) and all had an old valvular lesion. (2) Twelve patients had non-active RHD. They were aged 8–15 years (mean (SE) 11·6 (0·3) years) and had a mitral valve lesion (diagnosed by echocardiography) and a history of acute rheumatic fever according to revised Duckett-Jones criteria[5] six months or more before the study. They had no evidence of heart failure or rheumatic activity. (3) Fourteen healthy children were selected as a control group. They were aged 7–14 years (mean (SE) 10·4 (0·4) years). None of these children had a history of rheumatic fever or chronic or repeated tonsilitis, there were no valvular lesions, and there was a normal erythrocyte sedimentation rate. The characteristics of the subjects are shown in table 1.

Blood samples for the measurement of IL-2 and T cell subpopulations were taken before the start of any treatment.

Table 1 Characteristics of patients and control subjects

	Non-active RHD (n=12)	*Active RHD (n=13)*	*Controls (n=14)*
Mean (SE) age in years	11·5 (0·3)	9·2 (0·1)	10·4 (0·4)
Sex	9M 3F	5M 8F	10M 4F
Valve abnormality	Mitral valve only (n=11), mitral with aortic (n=2)	Mitral with tricuspid (n=3), mitral with aortic (n=2), mitral valve only (n=7)	No
Associated problems	No	Heart failure (n=6), arthritis (n=5), carditis and arthritis (n=1)	No
Mean (SE) antistreptolysin-O titre (Todd's units)	200·0 (19·8)	457·0 (149·1)	—
Mean (SE) total leucocyte count ($\times 10^9$ cells/l)	6·3 (0·4)	8·5 (1·2)[1]	5·0 (0·6)
C reactive protein	Negative	Positive	Negative

[1]p<0·05 There was a significant increase in total leucocyte count in active RHD in comparison with controls

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Table 2 T cell subsets in active and non-active RHD in comparison with control subjects. Data are mean (SEM)

	Active RHD (n=13)	*Non-active RHD (n=12)*	*Controls (n=14)*
CD3+ (pan T) cells in %	79·55 (0·94)*	78·20 (0·20)†	85·00 (1·11)
CD4+ (T helper) cells in %	53·95 (0·96)	48·00 (2·74)	53·65 (0·70)
CD8+ (T suppressor) cells in %	23·75 (1·19)†	28·83 (1·91)	32·23 (0·56)
H:S ratio	2·31 (0·14)†	1·71 (0·16)	1·66 (0·04)

*$p<0\cdot01$; †$p<0\cdot001$

There was a significant decrease in CD3+ and CD8+ in active RHD in comparison with controls There was no significant change in CD4+ in active and non-active RHD. Non-active RHD showed a significant decrease in CD3+ only There was a significant increase in H:S ratio in active RHD in comparison with controls

ASSAY OF IL-2

IL-2 was measured using a radioimmunoassay kit with radioactive iodine 125 supplied by Medgenix (Institut des Radio Elements, Fleurus, Belgium) according to radioimmunoassay principle.[6]

DETERMINATION OF T CELL SUBPOPULATION[7]

T cell subsets were determined by using fluorochrome conjugated reagents for T cell typing (Clonab monoclonal antibodies Biotest Diagnostics). Lymphocytes were separated from periopheral venous blood by Ficoll Hypaque gradient technique,[8] and adjusted to a concentration of 5 million/ml suspended in Hanks' medium. An aliquot of 100 µl of lymphocyte suspension was incubated with 200 µl of 1:20 prediluted and fluoroisothiocyanate labelled Clonab antibody (CD3+, CD4+, and CD8+) at 4°C for 30 minutes. This was washed twice with cold phosphate buffer saline (PBS), the pellet resuspended in 100 µl of PBS, and counted using fluorescent microscopy.

STATISTICAL METHODS

Our data were analysed by the two tailed *t* test for independent samples.[9] All the data are expressed as mean (SEM).

Results

Table 2 shows the T cell subsets in the children with RHD in comparison with controls. There was a significant decrease in CD8+ and CD3+ cells and significant increase in the helper: suppressor (H:S) ratio in children with active RHD when compared with the control group ($p<0\cdot001$, 0·01, 0·001 respectively); CD4+ cells showed a non-significant change in those patients. Patients with non-active RHD showed a significant decrease in CD3+ cells; this reflects the persistent decrease in CD3+ in patients with RHD whether the disease was active or non-active.

Table 3 shows IL-2 concentrations in RHD (active and non-active) in comparison with controls. We found a significant increase of IL-2 in active RHD in comparison with controls.

Table 3 IL-2 concentrations in active and non-active RHD in comparison with control subjects. Data are mean (SEM)

	Active RHD (n=13)	*Non-active RHD (n=12)*	*Controls (n=14)*
IL-2 (U/ml)	3·48 (0·62)*	1·85 (0·24)	1·257 (0·156)

*$p<0\cdot01$. There was a significant increase in IL-2 in active RHD in comparison with controls

Discussion

Generation of the cellular immune response depends upon two signals. The first one is the interaction of antigen or mitogen with macrophages; this results in their activation and the secretion of a soluble product called lymphocyte activating factor, now termed interleukin-1 (IL-1). This IL-1 is responsible for initiation of the second signal which results in two responses. (A) Activation of the T cell subpopulation, mainly T helper cells (CD4+), to express specific receptors for another soluble factor called T cell growth factor or IL-2. (B) The combination of the antigen with IL-1 and this induces the subset of T cells to secrete IL-2. The IL-2 molecules bind to IL-2 receptors on T helper cells and induce their proliferation.[10]

In patients with rheumatic fever and RHD, a depressed cellular immune response is now considered to have a central role in pathogenesis of rheumatic heart injury.[11] The immune system in rheumatic patients is challenged with an array of streptococcal antigens. The most important of these is blastogen A, which was found to have an effect on immunoglobulin synthesis and IL-1 and IL-2 formation.[4] In our study the significant increase of IL-2 ($p<0\cdot01$, table 3) was found in patients with active RHD when compared with controls. This significant increase in IL-2 in active RHD can be explained on the basis of initiation of the cellular immune response by streptococcal blastogen A (antigen) ending in secretion of IL-2.[10]

In a previous study IL-2 was found to increase the cell mediated cytotoxicity,[12] while other investigators suggested the presence of cytotoxic cell species in patients with RHD that could be activated by streptococcal antigens leading to cellular damage during active rheumatic fever.[13] Those cells that have such cytolytic activity were found to be natural killer cells,[14] usually the activity of natural killer cells was found to be triggered by IL-2.[15] Data from these studies support the fact that the significant increase of IL-2 in the serum of our rheumatic patients means that IL-2 is important in the abnormal immune response in RHD via its effect on natural killer cell activity and the increase in cell mediated cytotoxicity.

Also one of the abnormal immune responses that has been reported in RHD is the increased natural killer cell cytotoxicity.[2] This observation can be explained by our findings of increased IL-2 production in rheumatic patients ($p<0\cdot01$, table 3) as IL-2 is a lymphokine secreted from activated T lymphocytes and is responsible for the activity of natural killer cells, especially the cytotoxic character.[15] Thus we can suggest a sequence of events that is responsible for cellular damage in RHD: first stimulation of T lymphocytes by streptococcal antigens, this leads to secretion of IL-2, which results in increased natural killer cell cytotoxicity and the pathological changes in rheumatic patients.

In this study the Biotest Diagnostic Series of Clonab monoclonal antibodies (fluorochrome conjugated reagents for T cell typing) were used to determine T cell subsets in the studied groups of patients and controls. The CD3+, CD4+, and CD8+ monoclonal antibodies identify respectively all mature peripheral blood T lymphocytes, helper T cells, and suppressor T cells.

The present study revealed that there was a significant decrease in CD8+ and CD3+ and significant increase in the H:S ratio in children with active RHD as compared with controls ($p<0\cdot001$, $0\cdot01$, $0\cdot001$, respectively, table 2). CD4+ cells showed a non-significant increase in the active group when compared with the controls (table 2).

Other studies done on patients with acute rheumatic fever revealed significant depression of OKT1+ and OKT4+ with insignificant increase in OKT8+ cells.[16] Another in vitro study on tonsillar tissues from rheumatic patients revealed an increased CD4+:CD8+ ratio after exposure to streptococcal products.[17]

Our children with non-active RHD showed a significant decrease in CD3+ only (table 2, $p<0\cdot001$), with no significant change in IL-2, CD4+, CD8+, and the H:S ratio. These results imply that deficient CD3+ can be considered a constant finding in RHD whether active or not.

By comparing active and non-active RHD we observed a significant increase in IL-2 and the H:S ratio with a significant decrease in CD8+ cells. Thus a constant increase of IL-2 and a decrease in CD8+ cells were observed in patients with active RHD in comparison with both controls (tables 2 and 3, respectively) and the non-active RHD group. These data may add another constant finding that is related to rheumatic activity.

CONCLUSION

Deficient CD3+ cells can be considered a constant finding in patients with RHD, whether active or non-active. Also the significant increase in serum concentrations of IL-2 and the significant decrease in CD8+ cells can be considered as a finding related to rheumatic activity. Finally another study has been planned to evaluate tumour necrosis factor-α, interleukin-I B (IL-IB), and natural killer cell function in active and non-active RHD.

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Bronchoscopy in lipoid pneumonia

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Abstract

Forcible administration of rendered animal fat to infants is a tradition in south western Saudi Arabia. Accidental inhalation may result in a resistant form of lipoid pneumonia. A series of 24 cases of lipoid pneumonia, 22 of which were diagnosed by bronchoscopy with bronchial lavage and microscopic examination of the aspirate, are reported. The technique is described briefly and the results analysed. A high index of suspicion together with bronchoscopy and bronchial lavage of all cases of resistant or recurrent pneumonia is essential in areas such as ours for diagnosis of this condition.

(*Arch Dis Child* 1992,67:1376–7)

Since the first clinical report of lipoid pneumonia in 1925,[1] numerous cases have been reported in the world literature with a peak of reporting in the 1940s [2 3] With an increasing realisation of the deleterious effects of inhaled oil and the subsequent elimination of oily medication and nasal drops, there has been a dramatic decline in the occurrence of these cases.

In certain geographical areas, however, traditional customs and habits may predispose to the condition.[4–5] In the Tihamat Asir region of south western Saudi Arabia, rendered animal fat or ghee, called 'saman', is administered forcibly to neonates and infants by an elderly relative in the belief that it contributes to the well being of the child. Accidental inhalation of this animal fat with resulting lipoid pneumonia is consequently very common in this area. This paper highlights the role of bronchoscopy in the diagnosis and treatment of these cases.

Patients and methods

Children with resistant or recurrent pneumonia presenting over a three year period to Asir Central Hospital, the only tertiary care facility in the region, were studied. All the children were referred to the otolaryngologist by paediatricians. A detailed history including history of feeding of saman was obtained in each case. A chest radiograph was performed before bronchoscopy.

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Bronchoscopy was carried out by using a Storz ventilating paediatric bronchoscope of the appropriate size. Any secretion in the trachea or bronchi was aspirated using a sterile suction connected to a 'mucus trap'. When secretions were scanty, bronchial lavage was carried out by instilling 1–2 ml of sterile normal saline into the tracheobronchial tree and aspirating the contents after ventilating a few times. The aspirate was viewed macroscopically against a bright light and any oily droplets floating on the surface were noted. The aspirate was subjected to microbiological studies, including Gram and Ziehl-Neelsen staining, appropriate bacterial and fungal cultures, and special stain for fat (oil red 0). The gross bronchoscopic findings such as the state of the mucus membrane, the presence or absence of secretions, their nature, and presence of any other endobronchial pathology were noted. Chest radiographs were repeated within 24 hours of performing the bronchoscopy. The condition of the patient at follow up, particularly at one month after bronchoscopy, was also noted. All data were entered into a SPSS/PC computer program for analysis.

Results

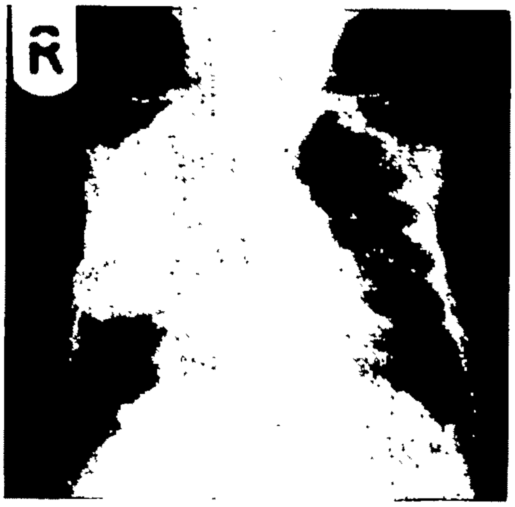
Out of a total of 115 pediatric bronchoscopies performed in Asir Central Hospital over a three year period, foreign bodies were found in 37 cases, recurrent or non-resolving pneumonias in 43 cases, and various forms of airway obstruction in 35 cases. Twenty out of the 43 cases (47%) of resistant or recurrent pneumonia and two out of 35 cases (6%) of airway obstruction tested positive for lipid by the method outlined above. None of the children with a foreign body tested positive. Two of our first cases were diagnosed by open lung biopsy because of our relative inexperience initially with the diagnostic techniques in lipoid pneumonia. Our series, therefore, had 24 cases of microscopically or histologically confirmed cases of lipoid in the tracheobronchial tree, making it one of the largest reported series of lipoid pneumonia.

Our patients had a median age of 9·5 months with a range of 1–132 months. Both sexes were similarly represented and all excepting one child were Saudis. The main clinical presentation is summarised in the table, and a representative chest radiograph is shown in the figure.

The reliability of history in the diagnosis of

Clinical features in 24 children with lipoid pneumonia

Feature	*No (%)*
Symptom	
Fever	15 (63)
Cough	17 (71)
Failure to thrive	2 (8)
Recurrent 'chest infections'	6 (25)
Signs:	
Respiratory distress	8 (33)
Cyanosis	2 (8)
Rales	10 (42)



Chest radiograph of a patient with lipoid pneumonia showing extensive consolidation of the right lung.

lipoid pneumonia was assessed in our series. A positive history of ghee administration was obtained in 21 of 24 (88%) cases. In six of these only repeated questioning produced this history. The remaining three patients with an uncertain history of ghee ingestion were severely handicapped children with cerebral palsy and feeding problems. In these cases milk aspiration as a cause of lipoid pneumonia could not be excluded with certainty.

Bronchoscopy in these children with lipoid pneumonia was not accompanied by any morbidity or mortality in our series. The chest radiograph taken 24 hours after bronchoscopy showed improvement in 19 cases, no change in three cases, and deterioration in none. However, this improvement was not sustained at one month after bronchoscopy as all patients needed further therapeutic measures such as corticosteroids. Thus bronchoscopy was less efficient as a therapeutic method than as a diagnostic tool as therapeutic benefits were not sustained over a period of time.

Discussion

Diagnosis of lipoid pneumonia has always posed challenges to the clinician. In earlier reports, diagnosis was often postmortem.[7] Some authors have found chest radiographs to be diagnostically useful.[5] However, we have not been able to demonstrate any distinct radiological patterns.[6] Although computed tomography has been advocated in the diagnosis,[8] patients with minimal and diffuse infiltration or with extensive fibrosis may not reveal the typical computed tomography densities of lipid. Fine needle aspiration and open lung biopsy seem to have also been advocated as diagnostic methods in lipoid pneumonia.[5] Apart from being invasive, the technique has the added disadvantage of being sometimes difficult to perform due to the inaccessibility of the lesion. Bronchoscopy with bronchial lavage has been previously employed and lipoid material demonstrated within macrophages and lying free in the aspirate.[5] We have at times observed lipoid material floating on the surface of the bronchial lavage even when examined by the naked eye. Bronchoscopy also gives the physician an opportunity to rule out other causes of recurrent bronchopneumonia such as neglected foreign bodies. The authors have preferred the use of a rigid ventilating bronchoscope, although a flexible bronchoscope may also be used for this purpose.

In centres where lipoid pneumonia is uncommon, it becomes important to establish the precise nature of the lipid by detailed chemical analysis to establish its source. However, in Saudi Arabia, where traditional practices account for the vast majority of the cases, such analysis is perhaps superfluous and not cost effective as the exact nature of the aspirated lipid is already known.

In areas where lipoid pneumonia is common, a high index of suspicion combined with bronchoscopy and bronchial lavage and staining of the aspirate for lipid seems to be a reliable and minimally invasive method for diagnosing the condition. If the bronchoscopy is inconclusive, other diagnostic methods may be needed. In children of 3 years of age and older, transbronchial biopsy may be helpful for establishing the diagnosis. We believe that open lung biopsy should be reserved for those few cases where the preceding less invasive methods are unhelpful.

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Causes of death in children diagnosed with non-Hodgkin's lymphoma between 1974 and 1985

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Abstract

An investigation has been undertaken of 479 deaths occurring up to the end of 1990 among 883 patients diagnosed with non-Hodgkin's lymphoma from 1974 to 1985 who were included in the population based National Registry of Childhood Tumours. The objectives were to perform a descriptive analysis looking particularly at the deaths not directly due to non-Hodgkin's lymphoma, to determine the frequency of the different causes of death and to study the trends over time.

Among the 476 patients with sufficient information for the cause of death to be established, these were: non-Hodgkin's lymphoma, 377 (79%); treatment related (other than second primary tumour), 86 (18%); second primary tumour, 10 (2%); and other, three (1%). The proportion of all deaths not directly due to non-Hodgkin's lymphoma increased from 15% for those diagnosed during 1974–6 to 32% for those diagnosed during 1983–5.

Among the 86 treatment related deaths, the more precise causes were bacterial infections, 26 (30%); viral and other infection, 14 (16%); metabolic, 19 (22%); renal, eight (9%); anaesthetic related, seven (8%); respiratory, four (5%); cardiac, three (3%); graft versus host disease, three (3%); and other, two (2%). Treatment related deaths from infection accounted for 27 (6%) of all patients diagnosed in 1974–9, and 13 (3%) in 1980–5. Treatment related deaths not due to infection occurred in 23 (5%) of those diagnosed in 1974–9 and 23 (6%) in 1980–5. Five treatment related deaths, including four anaesthetic related deaths, were identified as avoidable. Some of the deaths from metabolic and renal disease may also have been avoidable.

Only 11 deaths have been recorded more than five years after diagnosis, six being due to second primary tumours. As follow up is relatively short for patients diagnosed more recently, further deaths from second malignancies and treatment related cardiovascular problems may well occur.

A substantial number of children with non-Hodgkin's lymphoma die of treatment related causes. Deaths from infection have decreased in line with the overall improvement in survival rates. Other treatment related mortality has remained constant. Further improvements in survival for childhood non-Hodgkin's lymphoma will depend on maintaining the fine balance between the therapeutic value of intensive treatment and its potential harmful effects.

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A detailed analysis of survival rates for children in Britain with cancer diagnosed from 1971 to 1985, using data from the population based National Registry of Childhood Tumours (NRCT), has been published.[1] As expected, following the advances that have been made in treatment, this showed a dramatic improvement in survival in most diagnostic groups. One of the most striking results was the increase in the five year survival rate for children with non-Hodgkin's lymphoma from 24% in the mid 1970s to 70% in the mid 1980s. As survival rates improve it is increasingly important that the nature and frequency of the short and long term effects of cancer treatment are determined. The effects of treatment have often been studied at individual centres and in clinical trials, but few results are available from population based data. Long term effects have been the subject of a number of population based studies in Britain[2 3]; multicentre studies of late effects have been carried out by the Late Effects Study Group[4 5] and investigations are in progress by the late effects group of the United Kingdom Children's Cancer Study Group (UKCCSG).

In large population based studies it is difficult to obtain the necessary clinical details to determine the morbidity associated with the treatment of cancer. It is more practicable to study mortality and use the cause of death as an outcome measure. Obviously this will only detect the more severe effects of treatment, but none the less it is particularly important to have information on such effects. Hawkins *et al* have shown that studying the causes of death more than five years after diagnosis is an effective way of discovering severe treatment related effects and also potentially preventable deaths.[2] It is more difficult to determine the causes of earlier deaths as tumour and treatment effects can be difficult to separate. There have been few studies of deaths among children with cancer within five years of diagnosis. A small, single institution study of 37 deaths in children with acute lymphoblastic leukaemia concluded that five of the deaths occurring during induction or in primary remission, and not due to the malignancy itself, might have been prevented by appropriate diagnosis and treatment.[6]

The underlying cause of death recorded on the death certificate may well be unreliable.[7] Therefore it is necessary in a study of causes of death to glean as much information as possible from other sources, particularly hospital records.

The purpose of our study was to investigate the causes of death among children with non-Hodgkin's lymphoma included in the above mentioned analysis of survival rates. Our objective was to carry out a descriptive analysis, paying particular attention to the deaths not directly due to the original tumour and to determine the frequency of the different causes of death and also to observe any trends with time. We hoped to be able to identify potentially avoidable deaths. We chose to investigate children with non-Hodgkin's lymphoma as they represent a large group for which there has been a striking improvement in survival during the study period, and many of whom have received intensive treatment, often within the UKCCSG non-Hodgkin's lymphoma trials.[8,9]

Subjects and methods

The NRCT is a population based registry of cancer in children under the age of 15 years which covers the whole of Great Britain. Cases are ascertained from national and regional cancer registries, specialist regional children's tumour registries, notifications to clinical trials, and the UKCCSG. The registry receives death certificates for all deaths occurring in Britain under the age of 20 with a neoplasm coded as the underlying cause of death. At about five years from diagnosis the medical records of children in the registry are checked to confirm the diagnosis and to obtain a brief outline of treatment and follow up. The survivors, together with any children who have died but for whom no death certificate has been received, are flagged in the National Health Service Central Registers so that the NRCT receives a copy of the death certificate for any patient who has already died or who dies subsequently.

For this study non-Hodgkin's lymphoma was defined as all diagnoses in groups IIb–d in the Birch and Marsden classification,[10] including Burkitt's lymphoma and unspecified lymphoma. There were 883 children in the NRCT with non-Hodgkin's lymphoma diagnosed during 1974–85. Cause of death was studied in all 479 patients from the series who had died at any time from diagnosis up until the end of 1990.

The main source of information was the files held by the NRCT, which include death certificates, cancer registrations, UKCCSG registrations and follow up forms, and abstractions from general practitioner notes and hospital notes. When the information in the files was inadequate, and also in all instances where the circumstances of death were unusual or the death was judged not to be due to non-Hodgkin's lymphoma further information was sought. This was obtained from hospital notes and necropsy reports, from the files of the UKCCSG for a few children included in UKCCSG trials, and in a few instances by direct questions to the consultant.

The sources of information used on the 479 deaths in the study were: death certificates (472) (for seven patients who died abroad, no death certificate was available), routine follow up information (474), hospital notes (115), necropsy reports (69), and information from trials (seven).

The full series of 883 children was classified by primary site as follows: head and neck, 221; mediastinal and other thoracic, 187; intra-abdominal, 214; other specified sites, 78; and unspecified, 183, mostly children with widely disseminated disease at diagnosis in whom a primary site could not reliably be identified.

For each death the following information was collected: (A) the International Classification of Diseases eighth and ninth revisions[11 12] code for underlying cause of death on the death certificate, as coded by the Office of Population Censuses and Surveys for England and Wales and by the Information and Statistics Division of the Scottish Health Service. (B) The underlying cause of death, based on all available information, assigned by us to one of the following broad categories: original tumour (non-Hodgkin's lymphoma); treatment related (other than second primary tumour); second primary tumour; violent or accidental death; other unrelated medical condition; and insufficient information. This classification is based on the classification of cause of death used by Hawkins *et al* in their paper on late deaths.[2] (C) Evidence of presence of a tumour at time of death. (D) Site and date of first relapse.

The following conventions were used in assigning the deaths to these broad categories. Bronchopneumonia was often given as the cause of death in children who had gradually deteriorated with recurrent tumour; these deaths were all coded as tumour deaths rather than infection. If a child died from infection while receiving chemotherapy or within six months of stopping treatment the death was coded as treatment related. The death of one patient who had had a splenectomy and subsequently died of pneumococcal meningitis while in remission was also coded as treatment related. When death occurred from any cause and there was insufficient evidence to determine whether the patient had active disease at the time, then the death was coded as insufficient information. A second doctor reviewed all cases where the cause of death was coded as not due to the original tumour or where there was uncertainty about the cause of death.

Actuarial survival analysis was performed to determine the risks of dying from a particular cause of death in relation to type of treatment centre and whether the child had been included in a clinical trial. Children who did not receive any form of treatment or have a biopsy sample taken were excluded from the analyses of the mortality rates. In calculating rates for particular subcategories of cause of death, patients dying of causes other than that in question were censored at the time of death.

Results

Table 1 shows the causes of death as assigned by us using all available sources of information. There were three deaths for which the information available was insufficient to determine the cause of death. The numbers of deaths due to specific causes have been expressed as percentages of the remaining 476 deaths. Using all available sources we found that 377 (79%) died from non-Hodgkin's lymphoma and 99 (21%) died from other causes. Ten (2%) children died from second primary tumours; these consisted of six with acute myeloid leukaemia, two with

Table 1 Comparison of cause of death as coded by the Office of Population Censuses and Surveys on the death certificate and cause of death determined using all available sources of information

Cause of death on death certificate	Cause of death using all available information						
	Original tumour	*Treatment related*	*Second primary tumour*	*Accident*	*Other medical cause*	*Unknown*	*Total*
Non-Hodgkin's lymphoma	293	59	—	—	1	3	356
Acute lymphoblastic leukaemia	43	10	1	—	—	—	54
Unspecified leukaemia	3	1	—	—	—	—	4
Acute myeloblastic leukaemia	1	—	5	—	—	—	6
Other or unspecified neoplasm	24	8	4	—	—	—	36
Other cause	6	8	—	1	1	—	16
Died overseas	7	—	—	—	—	—	7
Total	377 (79%)[†]	86 (18%)[†]	10 (2%)[†]	1	2	3	479

[†] Number in parenthesis is expressed as a percentage of the 476 patients with known cause of death

osteosarcoma, and two with astrocytoma. One child died in a road traffic accident which was completely unrelated to the non-Hodgkin's lymphoma. The two children who died from other disorders had underlying immunodeficiencies (Wiskott-Aldrich and Bloom's syndrome) and it was judged that they died from these disorders rather than from the non-Hodgkin's lymphoma or its treatment.

Table 1 also shows the underlying cause of death as given on the death certificate. In most patients the death certificate code and the 'all sources' code were consistent. Nine of the 10 second malignancies had been coded correctly on the death certificate. There were 32 patients, however, where the death certificate gave the cause of death as a neoplasm other than non-Hodgkin's lymphoma or leukaemia (including a wide variety of tumours from thymoma to osteosarcoma) when the 'all sources' code was not a second primary tumour. Seventy eight of 86 deaths judged to be treatment related on the basis of all available evidence were coded on the death certificate as death due to the tumour. This can be partly explained by an anomaly in the International Classification of Diseases eighth revision[11] (used for coding deaths occurring before 1979) in which any death caused by treatment was coded to the disease for which the treatment was being given. This was amended in the International Classification of Diseases ninth revision[12] so that death caused by an untoward effect of treatment should be coded as such. In this study only one (3%) of the 35 treatment related deaths that occurred before 1979 was coded to a non-tumour cause on the death certificate, compared with seven (14%) of the 51 that occurred from 1979 onwards. Thus although the proportion of treatment related deaths assigned to a non-tumour cause increased with the change in coding practice, it remained low.

Table 2 gives an analysis of the 86 deaths considered to be due to treatment related factors. The subcategory with the largest number of patients was the group with infections; bacterial infections outnumbered viral and other infections by nearly two to one. There were no deaths from infection more than six months after chemotherapy had ended, except for one patient with pneumococcal meningitis thought to be related to a previous splenectomy. Other significant groups were the metabolic, anaesthetic, and renal deaths. Twelve of 19 metabolic deaths and four of eight deaths due to renal disease were in children with known abdominal primary tumours. These accounted for the fact that 26% of the deaths in this primary site group were treatment related compared with 18% overall. Table 2 also shows the number of deaths occurring during induction, in remission and in relapse. Over half (48; 56%) of the treatment related deaths occurred during initial induction and only 20 (23%) occurred during remission. A further 18 (21%) occurred in patients undergoing treatment for relapsed disease and many of these were probably unavoidable. Table 3 describes the causes of the 86 treatment related deaths in more detail.

There were 19 deaths among children who had previously received a bone marrow transplant. Of these, 11 died from relapsed non-Hodgkin's lymphoma. For the remaining eight children the causes of death were as follows: three graft versus host disease, three infections, one second primary tumour, and one cardiomyopathy.

Table 4 gives the number of deaths due to non-Hodgkin's lymphoma and other causes for four different time periods of diagnosis. The total number of deaths and the number of deaths from non-Hodgkin's lymphoma decreased over the study period, but the number of deaths from causes other than non-Hodgkin's lymphoma has remained nearly constant. Thus as a proportion of the total deaths, these increased from 15% (26/173) for the years of diagnosis 1974–6, to 32% (20/62) for 1983–5. The numbers in each category of deaths from causes other than non-Hodgkin's lymphoma are small but the data suggest that although the deaths from infection decreased with time, the treatment related deaths other than those from infection remained static within the period of follow up for the study.

Table 2 Nature of treatment related deaths

Subcategories	*No during first induction*	*No in remission*	*No in relapse*	*Total No (%)*
Infection				
Bacterial	11	5	10	26 (30)
Viral plus other	2	8	4	14 (16)
Metabolic disorder	19	0	0	19 (22)
Anaesthetic related	5	0	2	7 (8)
Renal disease	7	0	1	8 (9)
Cardiac disease	0	2	1	3 (3)
Respiratory disease	2	2	0	4 (5)
Graft-versus-host disease	0	3	0	3 (3)
Other	2	0	0	2 (2)
Total No (%)	48 (56)	20 (23)	18 (21)	86 (100)

Table 3 Details of treatment related deaths

Subcategory	*Detailed cause of death*
Infection—Bacterial	
Organism specified	9 *Escherichia coli* septicaemia
	2 pseudomonas septicaemia (one in perianal infection)
	2 with mixed Gram negative plus streptococcal septicaemia
	1 *Staphylococcus aureus* septicaemia
	2 pneumococcal meningitis (one in splenectomy patient)
	1 pseudomonas meningitis
Unspecified	5 septicaemia (one sialitis plus one perinanal infection)
	2 pneumonia
	1 peritonitis and colonic abscess
	1 meningitis
Infection—viral and other	
Specified	2 cytomegalovirus pneumonia
	2 pneumocystis pneumonia
	2 candidiasis
	2 varicella
	1 giant cell (measles) pneumonia
	1 herpes simplex
	1 herpes zoster
Unspecified	1 hepatitis
	1 meningitis
	1 encephalitis
Metabolic disorder	8 sudden death soon after laparotomy for extensive abdominal tumour (no chemotherapy)
	1 sudden death soon after bronchoscopy and biopsy, extensive tumour
	9 metabolic disturbance after first doses of chemotherapy
	1 during operation for paracentesis
Anaesthetic related	1 during anaesthetic induction for mediastinal biopsy (superior vena cava obstruction before operation)
	1 during anaesthetic for cervical lymph node biopsy (superior vena cava obstruction before operation)
	1 during anaesthetic for peritoneal tap and bone marrow
	1 inhaled gastric contents during anaesthetic for laparotomy for biopsy sample for abdominal mass
	1 during anaesthetic for laparotomy for biopsy sample of abdominal mass
	1 acute heart failure during operation for insertion of Hickman line, after first relapse
	1 during anaesthetic induction for removal of Broviac catheter Tracheal obstruction from undiagnosed relapse
Renal disease	1 renal failure from high dose cytosine
	1 renal failure following circulatory collapse, after an operation
	5 renal failures soon after laparotomy for abdominal tumour with renal disease or obstructive nephropathy
	1 renal failure, bilateral renal tumour, after only biopsy of shoulder mass
Respiratory disease	1 bilateral phrenic nerve palsies, after removal of mediastinal mass
	1 bilateral pneumothoraces while ventilated after lymph node biopsy
	1 respiratory arrest following thoracotomy for biopsy sample of mediastinal mass
	1 pulmonary fibrosis from radiotherapy in patient with ataxia telangiectasia
Cardiac disease	2 cardiomyopathy, 1 adriamycin, and 1 unknown aetiology
	1 superior vena cava obstruction, unknown aetiology, ?radiation
Graft versus host disease	3 patients
Other	1 acute brain degeneration six weeks after treatment started, ?drug toxicity
	1 toxic epidermal necrolysis during induction, ?tobramycin

There were only 11 late deaths (more than five years after diagnosis) in the study and this explains why actuarial survival analyses were not required for interpreting the data in table 4. Of these late deaths all but two were deaths other than from non-Hodgkin's lymphoma, six being caused by a second primary tumour. The distribution of the second primary tumour deaths by period of diagnosis, with relatively few second primary tumour deaths recorded so far among children diagnosed in 1980–5, can be explained by the fact that the latent interval for occurrence of secondary solid tumours is about 10 years. Therefore further late deaths from second malignancies are likely to occur. The latent interval for secondary leukaemias is four to six years and it therefore appears unlikely that many more of these will occur in this cohort.

Table 4. Total number of cases of non-Hodgkin's lymphoma diagnosed, deaths from non-Hodgkin's lymphoma and deaths from causes other than non-Hodgkin's lymphoma by period of diagnosis Three deaths with insufficient information have been excluded. Results given as No (%) of total number of cases diagnosed in each calendar period

	Year of diagnosis				
	1974–6	*1977–9*	*1980–2*	*1983–5*	*Total*
No of cases diagnosed	237	237	205	204	883
No of deaths due to non-Hodgkin's lymphoma	147 (62)	117 (49)	71 (35)	42 (21)	377 (43)
Total deaths not due to non-Hodgkin's lymphoma	26 (11)	32 (13)	21 (10)	20 (10)	99 (11)
Nature of deaths not related to non-Hodgkin's lymphoma					
Treatment related infection	12 (5)	15 (6)	7 (3)	6 (3)	40 (4)
Treatment related, not an infection	12 (5)	11 (5)	11 (5)	12 (6)	46 (5)
Second primary tumour	1	5	2	2	10 (1)
Other*	1	1	1	0	3

*Accident and other medical cause unrelated to tumour or its treatment

The 608 children who were diagnosed from 1977 (when the UKCCSG was formed) onwards and who received radiotherapy or chemotherapy for non-Hodgkin's lymphoma were classified according to whether they were treated at a paediatric oncology centre under a consultant who was a member of the UKCCSG and whether they were treated in the UKCCSG non-Hodgkin's lymphoma trials (including the T cell trial and patients registered with the UKCCSG as receiving the modified first study protocol). The five year survival rate for the 484 UKCCSG patients was 61% compared with 41% for the 124 patients treated elsewhere. The five year survival for the 241 trial patients was 63%, whereas for the 367 non-trial children it was 54%. The actuarial risks of treatment related deaths were not significantly different between UKCCSG and non-UKCCSG patients ($\chi^2=0{\cdot}39$ on one degree of freedom) nor between trial and non-trial patients ($\chi^2=0{\cdot}34$ on one degree of freedom).

Discussion

This study has confirmed that the official statistics available on cause of death as determined from death certificates are inadequate for detecting treatment related deaths, even after the modification to coding of treatment related deaths introduced with the ninth revision of the International Classification of Diseases. Therefore if mortality is to be used as an outcome measure to detect severe treatment related effects, it is essential that all available sources of information are used to determine the precise cause of death.

During the period 1974–85 treatment for non-Hodgkin's lymphoma became increasingly intensive, producing a marked improvement in survival. The percentage of patients dying from causes other than non-Hodgkin's lymphoma did not increase during the study period, but as a result of the dramatic decrease in the percentage of patients dying from non-Hodgkin's lymphoma the proportion of the total number of deaths accounted for by causes other than non-Hodgkin's lymphoma had doubled from 15% to 32%.

Treatment related mortality from infection nearly halved during the study period, presumably as a result of the improvements in general supportive management and increased availability of therapeutic and prophylactic antibiotics and antiviral agents.

It is of concern that the non-infective, treatment related mortality remained constant, but also reassuring that it has not increased. The largest subcategory within this group was the metabolic disorder deaths. These deaths all occurred soon after diagnosis, in children who were already unwell because of their tumour. It did seem, however, that medical intervention (an operation or starting chemotherapy) precipitated their deaths. Nearly half occurred after starting chemotherapy, mainly within 24 hours. The rest occurred during or soon after a diagnostic operation in children with extensive disease which affected the abdomen in all but one patient. Although tumour lysis can occur without any medical or surgical intervention there is also evidence that it can be precipitated by handling of the tumour during an operation.[13] Over the past few years there has been an increasing awareness of the careful initial management that is required for children with non-Hodgkin's lymphoma who have extensive disease. In particular the gentle introduction of chemotherapy and also the increased use of fine needle biopsy guided by ultrasound or computed tomography instead of laparotomy should reduce mortality from metabolic disturbances in future years.

The treatment related deaths from renal disease include six patients where there was renal disease or obstructive nephropathy from an abdominal tumour. These patients were included because an operation seemed to precipitate their deaths, which were thus possibly avoidable. The deaths related to an anaesthetic included two patients with compromised airways from superior venous cava syndrome which had been diagnosed before the operation, one patient with an undiagnosed mediastinal relapse causing tracheal obstruction, and one patient who inhaled gastric contents during the operation.

It is impossible to classify all the treatment related deaths into avoidable or unavoidable, but there are a few that almost certainly were avoidable. These included the four anaesthetic related deaths and also the patient who died of pneumococcal meningitis following splenectomy who was not receiving penicillin prophylactically. It is likely that some of the deaths related to metabolic and renal disease were also avoidable.

Most of the treatment related deaths in this study occurred within a few months of diagnosis. There were only two deaths from cardiomyopathy at 15 and 30 months after diagnosis. Children who have been treated with doxorubicin (Adriamycin) apparently remain at risk of death from cardiomyopathy for many years[14] and it is not yet possible to predict how many members of the study group will eventually die of treatment related cardiovascular problems. It is evident, however, that continued long term evaluation of these patients is essential not only for their care, but also for planning future chemotherapeutic treatment.

The occurrence of second primary neoplasms following childhood non-Hodgkin's lymphoma is already well documented, particularly among the patients included in the UKCCSG non-Hodgkin's lymphoma I study.[15] Of the 10 patients in this series, five have been reported previously[15 16]; the five previously unreported patients included three with acute myeloblastic leukaemia, one with osteosarcoma, and one with astrocytoma. This emphasises the point that the occurrence of second primary tumours in children treated for non-Hodgkin's lymphoma is a continuing problem and the long term risks of second primary tumours in patients who have received intensive treatment for non-Hodgkin's lymphoma are as yet unknown. Treatment for cancer with radiotherapy and chemotherapy, particularly the alkylating agents, is associated with an increased risk of developing a second primary tumour.[3–5] There is mounting evidence that epipodophyllotoxins are implicated in the occurrence of secondary leukaemias following treatment for a variety of adult and childhood cancers and especially non-Hodgkin's lymphoma.[17–19] This is of particular relevance as teniposide, one of the epipodophyllotoxins, was part of the protocol in the UKCCSG non-Hodgkin's lymphoma trials.[8 9] Children continued to be treated with these protocols after the official closure of the trials in 1983.

The difference in five year survival rate for children treated during 1977–85 in UKCCSG centres compared with those treated elsewhere was similar to that previously reported for 1977–84.[20] The risk of dying from a treatment related cause, however, did not vary significantly with the type of treatment centre or entry into trials. Despite apparently inadequate treatment outside paediatric oncology centres, the risk of death from a treatment related cause was just as high as for patients treated more effectively and presumably more aggressively in UKCCSG centres.

In conclusion, a substantial number of children diagnosed with non-Hodgkin's lymphoma during the period 1974–85 died from treatment related effects and as survival improves these deaths are becoming a larger proportion of the overall number of deaths. The number of deaths from infection is probably decreasing. Therefore further reductions in treatment related mortality are likely to depend on the prevention of deaths from metabolic and renal disorders, especially in children with intra-abdominal primary tumours, and in preventing deaths from complications of anaesthesia. As more is learnt about the aetiology of second primary tumours it may become possible to prevent some of them without compromising the present high survival rates for non-Hodgkin's lymphoma. Further improvements in survival for childhood non-Hodgkin's lymphoma will depend on maintaining the fine balance between the therapeutic value of intensive treatment and its potential harmful effects.

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Antiphospholipid antibody associated thrombosis in juvenile chronic arthritis

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Abstract

A child with systemic onset juvenile chronic arthritis (JCA) who developed a bilateral femuropopliteal vein thrombosis after plaster immobilisation following a tibial fracture is described. When the thrombosis was diagnosed, antiphospholipid antibodies detected either as lupus anticoagulant and anticardiolipin antibodies were found. This suggests that short term prophylactic antithrombotic treatment should be considered in antiphospholipid antibody positive JCA patients who require immobilisation after fractures of demineralised bones.

(*Arch Dis Child* 1992;67:1384–6)

There is evidence that patients with antiphospholipid antibodies, detected as lupus anticoagulant (LAC) or as anticardiolipin antibodies (aCL), have a tendency to thromboembolic phenomena, both arterial and venous. However, follow up studies have shown that only a minority of patients with these antibodies develop thrombosis,[1] and the real predictive value of antiphospholipid antibodies for developing thrombosis is not yet established.

Recently, we found a high prevalence of aCL in patients with juvenile chronic arthritis (JCA).[2] However, we failed to demonstrate any relationship between aCL and those clinical manifestation usually associated with these antibodies. Moreover, to the best of our knowledge, no case of antiphospholipid antibody associated thrombosis reported in children had JCA.[3]

We describe here a child with systemic onset JCA who developed a bilateral femuropopliteal vein thrombosis after plaster immobilisation following a tibial fracture. At the time when the thrombosis was diagnosed, we found the presence of both LAC and aCL. Our case suggests that antiphospholipid antibodies may be an important cofactor for developing thrombosis in children with JCA when another potentially thrombophilic event occurs.

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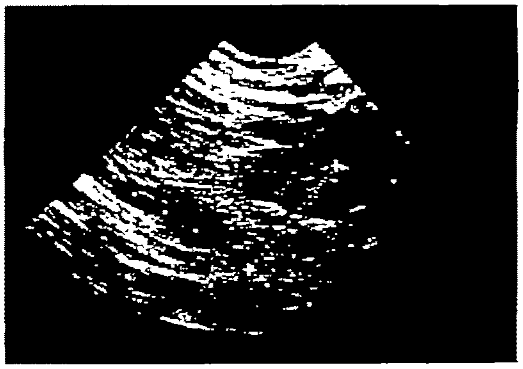
Case report

In 1978 a boy, aged 4 years, presented with high spiking fever, rash, and polyarthritis. A diagnosis of systemic onset JCA was made in our department in 1980 and the child was treated with salicylates, auranofin and, during systemic and/or articular exacerbations, with cycles of low dose daily prednisone. Over the following years the disease remained active with persistent systemic manifestations and severe polyarthritis. In the meantime, the boy progressively developed multiple limitations of joint motion and diffuse radiological signs of articular damage. During this time he was seldom referred to our department and the dosage and regimen of low dose prednisone were managed by his parents at home independently, according to his daily symptoms. In September 1988, 10 years after onset, he had a cushingoid appearance, with multiple limitations of joint motion and severe difficulty in walking, and persistence of fever, rash, and polyarticular synovitis. Skeletal radiograms revealed a dorsolumbar vertebral collapse, worsening of articular erosions, particularly at the hips, and diffuse osteoporosis. Steroids were suspended and low dose oral methotrexate (10 mg/m^2/week) was started in association with salicylates.

In May 1990 the child was involved in a road accident and suffered a multiple fracture of the right tibia. He was treated elsewhere with exceedingly prolonged (five months) plaster immobilisation of the right leg. After plaster removal a generalised swelling of the right leg with cutaneous erythema and local pain was noted. The child came back to our department three months later. Physical examination showed swelling of both legs, with the circumference of the right 3 cm greater than the contralateral, slight cutaneous redness and, on the right side, a subcutaneous venous reticulum and oedema of the dorsum of the foot. Examination revealed multiple limitations of joint motion and active synovitis at wrists, knees, and ankles.

Pertinent laboratory investigations were as follows: white cell count 13×10^9/l with normal differential, haemoglobin concentration 109 g/l, platelet count 833×10^9/l, erythrocyte sedimentation rate 60 mm in the first hour, prothrombin time 50% (normal range 70–110%), partial thromboplastin time 75·4 seconds (normal <26 seconds). Blood urea, creatinine, glucose, electrolytes, and serum complement



Doppler ultrasonography of the left leg showing a thrombotic occlusion of the popliteal vein.

concentrations, and urinalysis were normal. Rheumatoid factor and antinuclear, antiextractable nuclear antigen, and antimitochondrial antibodies were absent. The LAC test was positive and low titre (12 arbitrary units) of aCL of the IgG isotype were found by enzyme linked immunoabsorbent assay. Both LAC and aCL tests were performed as previously described.[4] A Doppler ultrasound examination of the lower limbs showed an extensive, bilateral thrombosis of both femoral and popliteal veins (figure). The child was discharged with weekly subcutaneous heparin calcium (Calciparine, Sanofi) and was then lost to follow up.

Discussion

We have reported a child with systemic onset JCA who developed an extensive deep vein thrombosis after a five month period of plaster immobilisation following a tibial fracture. When thrombosis was diagnosed, three months after plaster removal, both LAC and low titre IgG aCL were detected.

Only a few data exist on antiphospholipid antibodies in childhood. Our recent studies have shown a high frequency of aCL in children with JCA[2] but no aCL associated thrombotic events have been observed in these cases. Therefore, in JCA, the real predictive value of aCL antibodies for developing thromboembolic events is weak, and in no way is antithrombotic prophylaxis indicated on the unique basis of a positive aCL assay.

It should be noted, however, that the clinical experience on aCL in adults has shown that associated thrombophilic factors such as smoking and use of oral contraceptives may enhance the risk of thrombosis.[5] Prolonged immobilisation is well known to be associated with an increased risk of thromboembolism, and its association with antiphospholipid antibodies might have lead to deep vein thrombosis in our child.

This observation suggests that when children with JCA need immobilisation, such as after fractures of demineralised bones, the presence of antiphospholipid antibodies should be investigated as they may act as additional risk factors for thrombosis.

It should be noted that in our patient both LAC and aCL were detected and that it has been suggested that LAC represents a more specific, although less sensitive, marker of the thrombotic risk than aCL.[6]

In conclusion, our report suggests that short term prophylactic anticoagulant and/or antiaggregant treatment should be considered in those antiphospholipid antibody positive children with JCA who require immobilisation, particularly if circulating LAC is present.

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Severe anaemia and ileocolic anastomotic ulceration

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Abstract

Two children are described with anaemia from ileocolic anastomosic ulceration as a late complication of surgery in the newborn period. The anastomosis was revised in each case but in one child there was early recurrence of ulceration.

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Ulceration at the site of an ileocolic anastomosis as a late complication of neonatal surgery has been described, but is probably underrecognised. Rational management is hampered by lack of understanding of the underlying aetiology of the condition. We report our experience in two children with this unusual problem.

Case reports

CASE 1

A boy of 25 weeks' gestation required ventilation for respiratory distress, but after extubation he was established on full enteral feeds. At 9 weeks of age he developed abdominal distension and bloody diarrhoea and an abdominal *x* ray film confirmed necrotising enterocolitis. Despite medical management his condition deteriorated, necessitating laparotomy. A diseased segment of ileum was resected and a cutaneous enterostomy fashioned, after which he made a good recovery. Two months later radiological investigation confirmed two colonic strictures that were resected and an ileocolic anastomosis performed. He was discharged home at 6 months of age, on full enteral feeding, and followed up at his local hospital.

He was referred to the surgical unit at the age of 7 years for investigation of anaemia. He had no symptoms, was on the third centile for both height and weight, and was passing two normal stools each day. Despite recent transfusion, investigation revealed a microcytic hypochromic anaemia, with a haemoglobin concentration of 65 g/l. Testing for faecal occult blood gave a strongly positive result. An upper gastrointestinal endoscopy and barium meal both gave normal results, but at colonoscopy the mucosa at the site of the ileocolic anastomosis was seen to be reddened and friable. A ^{99m}Tc-labelled red cell scintiscan suggested bleeding was occurring from this region. At laparotomy, perianastomotic ulceration involving both small bowel and colonic mucosa was confirmed. There was no evidence of stricture. The ulcerated segment of bowel was resected and the anastomosis revised. Histological examination revealed non-specific ulceration.

Three months later his haemoglobin concentration fell to 60 g/l; colonoscopy showed fresh bleeding from recurrent ulceration at the site of the revised anastomosis. Treatment for six weeks in turn with oral sulphasalazine 40 mg/kg/day, sucralfate 40 mg/kg/day, mesalazine 40 mg/kg/day, and ranitidine 30 mg/kg/day failed to stop bleeding. The anastomosis was shown radiologically to be inaccessible to steroid enema

Serum gastrin concentration was not raised (26 pmol/l, reference range <40); a hydrogen breath test was negative and empirical treatment for bacterial overgrowth with two weeks of metronidazole and trimethoprim had no influence on further blood loss. Over a six month period he required transfusion every three weeks. After discussion with parents it was decided that an ileostomy might stop blood loss and improve quality of life, and this was subsequently performed. Over the next 12 months his haemoglobin was maintained at a normal concentration, although large volume ileostomy losses were an unforeseen complication.

CASE 2

A boy was born at term with gastroschisis. Primary closure was not possible and part of the bowel became necrotic. Altogether 50% of the small bowel was resected and an ileocolic anastomosis fashioned. The gastroschisis was eventually closed on day 10, with a porcine dermis patch. He was discharged home at the age of 9 weeks on a modular feed based on comminuted chicken. By the end of the first year of life he was tolerating soya milk and a variety of solids, although his weight gain was poor and stools continued to be loose.

At the age of 5 years he presented with bouts of abdominal pain and melaena. Investigation revealed a haemoglobin concentration of 50 g/l with an iron deficient picture. The anaemia recurred despite transfusion and he was referred back to the surgical unit for investigation. The following studies gave normal results: upper gastrointestinal endoscopy, colonoscopy, contrast enema, radioisotope scan for Meckel's diverticulum, and ^{99m}Tc-labelled red cell scintiscan. Serum gastrin concentration was normal (38 pmol/l). Treatment with cimetidine 20 mg/kg/day for two months did not prevent anaemia. He underwent laparotomy and chronic ulceration was discovered at the site of the ileocolic anastomosis. There was no evidence of stricture and the anastomosis was revised; histology showed non-specific ulceration. Eighteen months later he remains well with no recurrence of gastrointestinal blood loss.

Discussion

Ileocolic anastomosis may be necessary in necrotising enterocolitis, intussusception, or congenital abnormalities of the bowel. Extensive resection of ileum sometimes results in diarrhoea and malnutrition particularly if the ileocaecal valve is lost, or if in combination with partial colectomy.[1] Perianastomotic ulceration appears to be a rare complication of ileocolic anastomosis in the newborn period presenting with severe anaemia up to 12 years after surgery.[2 3] Colonoscopy is the most helpful investigation. The aetiology of the ulceration remains obscure and rational treatment problematic. Histological appearances give no clue to underlying mechanisms. Ulceration has not been related consistently to either anastomotic stricture or type of suture material. Blind loop syndrome with small bowel bacterial overgrowth and deconjugation of bile salts has been linked with mucosal ulceration.[4] Classical symptoms include chronic obstruction, malnutrition, and malabsorption leading to growth failure.[5] Both our patients were growing normally and neither was found to have blind loops at operation. On the basis that local factors such as bowel flora or pH might be playing a part, we gave treatment with broad spectrum antibiotics and H_2 blockers, but with no cessation of bleeding. Although it has been reported that sulphasalazine can prevent bleeding,[1] no such effect was seen in our patient given anti-inflammatory agents. Due to the severity of bleeding and requirement for repeated transfusions we chose revision of the ileocolic anastomosis. Unfortunately, recurrent ulceration rapidly followed, a complication previously described.[3] An ileostomy successfully stopped bleeding but large volumes of effluent have created a new problem suggesting that the remaining small bowel is predominantly jejunum.[6] Anastomotic revision appears to have been more successful in our second case.

If absence of the ileocaecal valve is a critical factor in aetiology perhaps the development of surgical techniques aimed at reconstruction of valve mechanism might offer a hope of cure. Unfortunately, the presence of a valve does not altogether preclude the possibility of anastomotic ulceration.[3] A rational approach to management must depend on a future understanding of the aetiological mechanisms concerned, but long term follow up of children who have undergone ileocolic anastomosis in the newborn period is clearly essential.

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PERSONAL PRACTICE

Intercurrent illness in inborn errors of intermediary metabolism

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Abstract

Metabolic decompensation may occur in patients with disorders of intermediary metabolism during intercurrent illness. To prevent complications it is normal practice to change the diet to an 'emergency regimen'. The mainstay of this is a high carbohydrate intake, using soluble glucose polymer, given as frequent drinks by day and during the night. Additional therapy is given for some disorders. Practical details of the treatment are outlined.

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Diet is the mainstay of treatment for many inborn errors of intermediary metabolism.[1] Patients are stabilised on a diet appropriate for their disorder that will provide them with sufficient nutrients and energy to grow and develop normally. However metabolic stress such as intercurrent infections may precipitate decompensation and cause complications. To prevent these it is common for the diet to be changed to an 'emergency regimen'. The purpose of this paper is to outline the principles and practice of these regimens.

Principles

During illness and fasting various metabolic adaptations occur.[2]

(A) PROTEIN CATABOLISM

There is constant turnover of tissue protein and overall, the rate of protein synthesis exceeds that of breakdown so there is net gain and hence growth.[3] However, during illness the rate of protein breakdown normally exceeds that of synthesis with net production of amino acids and an increase in their irreversible catabolism. The nitrogen moiety of amino acids is converted to ammonia and then to urea. The carbon skeleton of amino acids is progressively catabolised to form fuels for energy production including acetyl CoA, pyruvate, and intermediates of the Krebs cycle.

(B) SUBSTRATES FOR ENERGY PRODUCTION

Glucose is a major fuel for energy metabolism but glycogen reserves for glucose production during fasting are relatively limited in children. To maintain a supply of substrate for energy production and protect glucose supply to the brain it is necessary to mobilise alternative fuels, including free fatty acids, ketones, and gluconeogenic precursors.

On fasting, as glucose concentrations slowly fall, there is a decrease in the insulin:glucagon ratio with mobilisation of fatty acids from adipose tissue stores. Free fatty acids can be utilised by many tissues, such as the heart and skeletal muscle, but they cannot enter the brain. In the liver, free fatty acids are partially oxidised to ketones which are water soluble and can enter the central nervous system. Alanine and other amino acids from muscle catabolism and glycerol from lipolysis are substrates for gluconeogenesis.

The purpose of the emergency regimen is to prevent the changes that occur with fasting. The aim is to reduce protein catabolism and hence the accumulation of potentially toxic metabolites. By giving an adequate supply of glucose the mobilisation of alternative fuels is also reduced.

Practical aspects of emergency regimens

The core of the emergency regimen is essentially similar for all disorders. A solution of glucose polymer is given as the major source of energy because it is simple, palatable, and usually well tolerated. Fat emulsions can provide additional energy, but these are less well tolerated; fat delays gastric emptying and is more likely to cause vomiting so we do not use them routinely. It is also contraindicated in some disorders, such as inborn errors of fatty acid oxidation. In most instances we would start by giving feeds orally. There are important advantages to oral feeding. It can be started at home; more glucose can be given than by peripheral intravenous infusions and medicines can be given. This can be important as intravenous preparations of the medicine are often not readily available. If oral feeding is not possible, nasogastric feeding, either bolus or continuous, should be tried before intravenous therapy for the same reasons.

The concentrations and volumes of solution given will depend on the age of the child. Relatively higher volumes and lower concentrations are used in infants compared with older children (table). Insufficient fluid combined with high concentrations of glucose polymer that can cause diarrhoea may exacerbate the effects of illness. If the child is likely to become dehydrated it is advisable to give an oral rehydration solution supplemented with glucose

Emergency regimen

Age (years)	*Glucose polymer concentration*		*Daily volume*	*Frequency*
	%	*kcal/100 ml**		
0–1	10	40	150–200 ml/kg	Initially every two hours night and day
1–2	15	50	95 ml/kg	
2–6	20	30	1200–1500 ml	
6–10	20	30	1500–2000 ml	
>10	25	100	2000 ml	

*1 kcal=4 18 kJ

polymer to the required concentration. (Practice note: oral rehydration solutions do *not* contain sufficient glucose on their own.) The solution is given orally as small frequent drinks or enterally via a nasogastric tube, normally at intervals of two hours night and day. This is usually well tolerated. It is particularly important not to allow the child to go for long periods (>4 hours) between drinks during the night.

Parents are taught to make solutions using an appropriate sized scoop which is quick and easy. These solutions can also be frozen and thawed when needed at home or in hospital. All proprietary liquid glucose polymer solutions have a concentration of 50% carbohydrate or more, for example, Fortical (Cow and Gate) and Liquid Maxijul (Scientific Hospital Supplies), and are not suitable for an emergency regimen unless diluted to an appropriate concentration. In our experience these are less palatable and more likely to induce vomiting or diarrhoea if given undiluted.

In some children the first symptom of any illness is refusal to eat or drink. If so, we often teach the parents how to use a nasogastric tube at home, thereby reducing the need for a hospital admission.

If the child has occasional vomits, it may still be possible to feed orally by giving the drinks as frequent sips (for example 10 ml every 10 minutes) or as a continuous nasogastric feed either at home or in hospital. However, if the child is vomiting frequently or is obviously unwell then intravenous therapy is essential. Concentrated glucose solutions should be used: 10% dextrose by peripheral drip or more concentrated through a central line. Hyperglycaemia may develop so blood glucose concentrations should be monitored regularly.

Instructions for parents

Many parents have difficulty in knowing both when to start the emergency regimen and exactly what to do. To overcome this it is our practice to teach a three stage approach.

(1) If the parents are uncertain whether their child is unwell (or just tired) because they appear lethargic, irritable, or off colour then an emergency regimen drink should be given. Next, a conscious decision is made to reassess the child within one to four hours, depending on the age and disorder. In some children it is possible to monitor the disorder by using simple tests at home. These are discussed later under the individual disorders.

(2A) If on review the child has improved, the normal diet is resumed. (B) If on reassessment there is no improvement the full emergency regimen of drinks every two hours should be started. There is some flexibility in the frequency of the drinks particularly in the older children and during recovery. During illness most children will automatically stop eating the normal diet, and once the child starts to improve the usual diet is gradually reintroduced.

(3) If the child is refusing to take the drinks, is vomiting frequently, or becoming encephalopathic then they should be admitted to hospital for assessment. The parents need to be aware of and recognise clinical signs of deterioration. Of particular importance is the ability to recognise encephalopathy with the child becoming less responsive, often with a glazed look.

Parents may face difficulties if the child does not take all the recommended volumes of feed. The quantities necessary vary both with the underlying inborn error and the intercurrent illness. It is particularly important that patients with maple syrup urine disease and methylmalonic acidaemia should have close to the recommended volumes (see below). By contrast those with glycogen storage disease may be controlled satisfactorily with smaller volumes. Patients with gastroenteritis will in general need more fluid than those with upper respiratory tract infections.

It should be emphasised that the basic emergency regimen must not be continued for long periods of time because it does not provide adequate nutrition and will cause nutritional deficiencies. Early clinical signs of such deficiencies include skin rashes (particularly at the site of adhesive tape for nasogastric tubes). Most patients can be gradually returned to their usual diet within a few days.

When the diet is being reintroduced additional high carbohydrate drinks are given until the normal diet is re-established. In infants, additional glucose polymer is added to the formula feed. For patients on low protein diets the protein intake is usually increased daily, giving one quarter, one half, three quarters of the usual intake, resuming the normal protein allowance by day four.

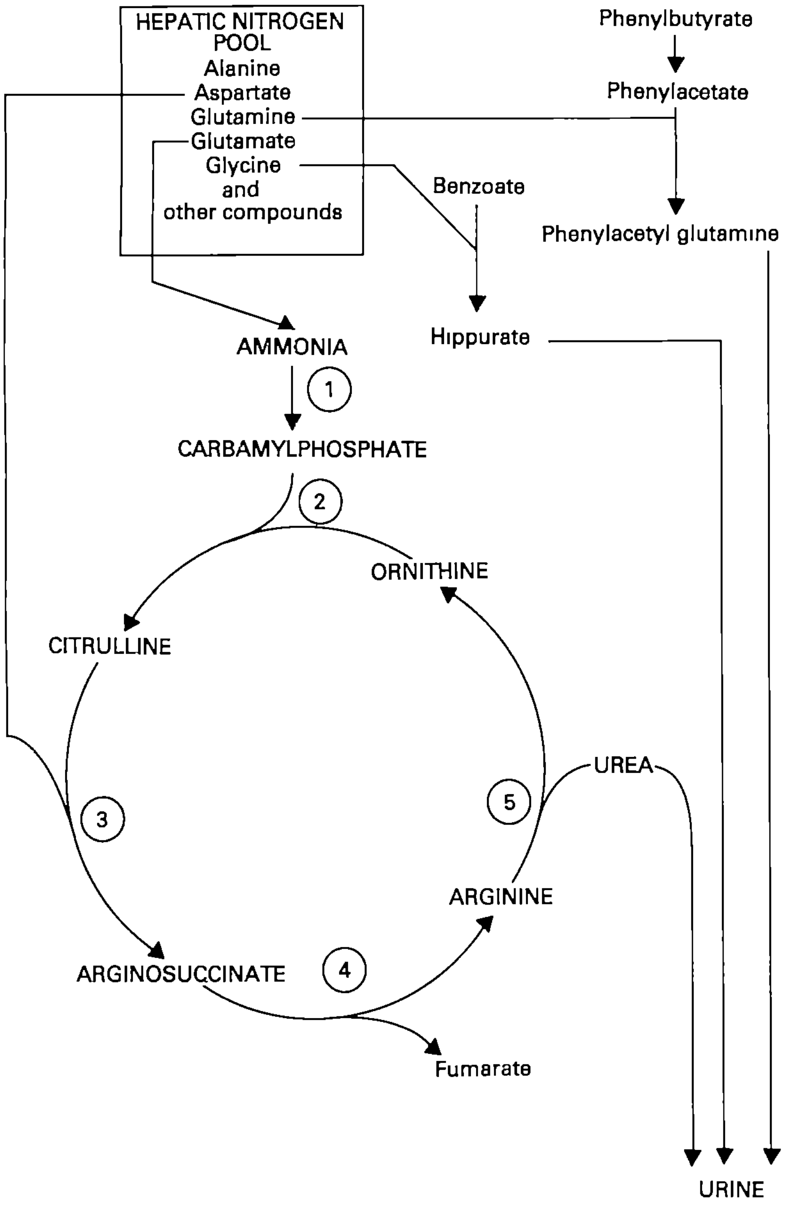
Whenever the child has been ill it is usual for us to discuss the emergency regimen carefully, checking that the parents knew what to do and that the emergency regimen meets the needs of their child. It is important to recognise that the course of these disorders is often unpredictable. The children may have a serious infection without any problems, but then develop severe decompensation after apparently minimal stress; therefore the need for careful management of all intercurrent illness.

Specific treatment

This basic emergency regimen is suitable for disorders of carbohydrate metabolism including glycogen storage diseases, fructose-1, 6-diphosphatase deficiency, and 'ketotic hypoglycaemia'. However, in other metabolic disorders the emergency regimen is combined with specific treatment.

MAPLE SYRUP URINE DISEASE (MSUD)

In MSUD the branched chain ketoacid dehydrogenase is defective. This enzyme is the second step on the catabolic pathway of the three branch chain amino acids (BCAA): leucine, isoleucine, and valine. This pathway is the major route for disposal of the BCAA. As it is blocked in MSUD[4] the BCAA and respective ketoacids accumulate and are responsible for the encephalopathy. Losses of BCAA and ketoacids in the urine and through other pathways are low[4] so the only way to reduce plasma concentrations is for the BCAA to be incorporated into protein. The objective of treatment during illness is to increase the rate of protein synthesis by giving a high energy intake as glucose with or without fat. Although the rate of protein synthesis may increase initially the concentration of the essential amino acids other than the BCAA will soon become rate limiting. To prevent this supplements of the BCAA free amino acids should be given.[5] Our aim is to provide the full energy requirement and the child's usual quantity of BCAA free supplement. This is not always possible orally, particularly if the child is vomiting. A useful alternative is continuous nasogastric feeding of Maxamaid MSUD (Scientific Hospital Supplies, see appendix) supplemented with extra glucose polymer. We have successfully used this to treat patients with MSUD who have been unable to tolerate bolus feeds. Parenteral nutrition, using a BCAA free amino acid solution, is an alternative if enteral feeding fails but this is available in few centres. Regular daily quantitative measurements of the BCAA are essential to monitor progress and to determine when protein can be reintroduced.



Hepatic nitrogen metabolism. Urea, the major product of nitrogen catabolism, is synthesised within the urea cycle from aspartate and ammonia. Defects of each step in the cycle have been identified. (1) Carbamylphosphate synthetase deficiency (2) Ornithine carbamyltransferase deficiency. (3) Arginosuccinate synthetase deficiency (citrullinaemia). (4) Arginosuccinate lyase deficiency (arginosuccinic aciduria). (5) Arginase deficiency. In these disorders sodium benzoate and sodium phenylacetate (or phenylbutyrate) are used to reduce the flux in the urea cycle. Benzoate is conjugated with the glycine to form hippurate and phenylacetate conjugated with glutamine to form phenylacetyl glutamine. Both of these compounds are rapidly excreted in the urine reducing the accumulation of ammonia and amino acids

Once the plasma leucine concentration falls below 800 μmol/l some leucine usually as natural protein can be reintroduced, and is increased to the usual intake according to the plasma concentrations. Our aim is to keep plasma leucine between 200–700 μmol/l. During the recovery phase concentrations of the isoleucine and valine may fall to low concentrations and become rate limiting for protein synthesis. Supplementation of these amino acids then becomes necessary, in doses of 50–300 mg/day. To do this a solution of the amino acids is made (providing 100 mg of amino acid in 10 ml) and the required amount added to the feed. We do not routinely give valine and isoleucine supplements[5] as not all patients need them and this practice could cause imbalance in amino acid concentrations. Hypokalaemia may develop during the recovery phase.

PHENYLKETONURIA (PKU)

Many centres do not give patients with PKU an emergency regimen or monitor plasma phenylalanine concentrations during illness. However with increasing emphasis on improving metabolic control, an emergency regimen is likely to be necessary. It should be similar to that used in MSUD.

UREA CYCLE DISORDERS

The urea cycle converts waste nitrogen into urea, via a series of enzymes (figure). Inborn errors have been identified for each step and may cause accumulation of ammonia and glutamine which are neurotoxic and may cause a severe encephalopathy.

Patients are treated with a low protein diet and medicines which promote nitrogen excretion via alternative pathways. Sodium benzoate is most widely used. It is conjugated with glycine to form hippurate, 1 mole of nitrogen being excreted for each mole of sodium benzoate given. Phenylbutyric acid can also be given either as the free acid or the sodium salt but is less palatable. Phenylbutyrate is metabolised in vivo to phenylacetate, and is more effective than benzoate because it is conjugated with glutamine to form phenylacetylglutamine, 2 moles of nitrogen being excreted for each mole of phenylbutyrate given.

During illness protein breakdown may cause rapid accumulation of ammonia and glutamine. In addition to the basic emergency regimen the usual medication should continue to be given. Both sodium benzoate and phenylbutyrate are given in a dose of 250 mg/kg/day but can be temporarily increased to 500 mg/kg/day during illness.

Another consequence of these disorders is that arginine becomes an essential amino acid (except in arginase deficiency). During illness the normal arginine supplements, 100 mg/kg/day, should be given. In citrullinaemia and argininosuccinic aciduria, arginine should be given in larger doses of up to 700 mg/kg/day to replenish ornithine that is not reformed as a result of the metabolic block. All the medication should be given in frequent small doses. If the child cannot tolerate oral fluids or medicines sodium benzoate, sodium phenylacetate, and arginine should be given intravenously.

Patients should be monitored with regular measurement of plasma ammonia and quantitative plasma amino acids. Protein can be reintroduced once the ammonia is less than 80 μmol/l.

Occasionally it can be difficult to reintroduce protein without inducing hyperammonaemia and in these cases an essential amino acid supplement (for example Dialamine, Scientific Hospital Supplies, see appendix), can be given. This will promote both protein synthesis and the reutilisation of nitrogen to form non-essential amino acids thereby reducing ammonia accumulation.

TYROSINAEMIA TYPE I (FUMARYLACETOACETASE DEFICIENCY)

Tyrosinaemia type I is caused by a deficiency of fumarylacetoacetase, the last enzyme of the catabolic pathway of tyrosine, with resultant accumulation of succinylacetone and related metabolites. Patients are usually treated with a diet restricted in tyrosine and phenylalanine. Although it is not common to use an emergency regimen in this disorder, decompensation of liver function and deterioration of neurological function can follow intercurrent infection. It is probably beneficial that an emergency regimen is given to reduce these problems. The patients may also need appropriate treatment for liver failure.

ORGANIC ACIDAEMIAS

(a) Propionic and methylmalonic acidaemia

Propionic and methylmalonic acidaemia are caused by inherited enzyme defects in the pathways of propionate catabolism. Propionate is formed from several sources including the amino acids isoleucine, valine, methionine, and threonine, by anaerobic bacterial fermentation in the gut and catabolism of odd chain fatty acids. Although amino acids are widely regarded as the major source of propionate, only about 50% of propionate is derived from breakdown of amino acids.[6] About 20% is derived from the gut[6] and the rest (30%) probably from the catabolism of odd chain fatty acids.[7] The toxic metabolites and the mechanisms responsible for all the clinical problems are not well understood but the aim of treatment is to reduce the accumulation of propionate by diminishing production and increasing disposal.

In addition to the standard emergency regimen to reduce protein breakdown and amino acid catabolism, propionate production from the gut is reduced by giving metronidazole (or an alternative antibiotic). The removal of propionyl groups is enhanced by giving L-carnitine. This forms propionyl carnitine which is excreted in the urine. Carnitine is given either orally or intravenously in a dose of 100 mg/kg/day. Higher doses have been used although their value and complications have not been assessed critically. In methylmalonic acidaemia there is usually massive excretion of methylmalonate in the urine with obligatory simultaneous losses of sodium and potassium. These patients also have a concentrating and acidification defect in the kidney[8] so it is essential to give sufficient fluid with supplements of sodium bicarbonate (2–3 mmol/kg) to replace sodium loss and reduce the acidosis. Patients may also need potassium supplements particularly during the recovery phase.

It may be helpful to monitor the patient's condition by measuring urine ketones but in our experience the parents' clinical judgment is as useful for most children.

It is important to reintroduce protein early (within two to three days) to prevent protein deficiency and additional problems such as rashes and vomiting.

(b) Isovaleric acidaemia

Isovaleric acidaemia is due to a deficiency of isovaleryl-CoA dehydrogenase, the third step in the pathway of leucine degradation. Isovaleric acid accumulates and its excretion in the urine can be increased by giving L-carnitine (100 mg/kg/day) and glycine (250 mg/kg/day). These are conjugated to form isovalerylcarnitine and isovalerylglycine respectively, both being rapidly excreted in the urine. This treatment can be given orally or intravenously.

(c) Other organic acidaemias (for example, 3-methylcrotonylglycinuria, glutaric aciduria type I)

In addition to the standard emergency regimen, L-carnitine is widely used to increase the removal of acyl groups, although controlled studies of its efficacy are lacking.

DISORDERS OF FATTY ACID OXIDATION

Inborn errors at several steps in the pathway of fatty acid oxidation are now well described, the most common is medium chain acyl CoA dehydrogenase deficiency. To prevent illness in these patients the standard emergency regimen is used. It is important to stress early use of the emergency regimen to inhibit mobilisation of fatty acids, particularly in long chain disorders because decompensation may be rapid. Additional treatment with L-carnitine is widely used but is somewhat controversial; there is little detailed critical work. Carnitine is essential in primary systemic carnitine deficiency and may be helpful in reversing decompensation in disorders of medium chain fatty acids. In theory carnitine in long chain fatty acid oxidation disorders might be harmful, by promoting the uptake of long chain fatty acids into mitochondria. Its use requires more evaluation.

Blood glucose is often used to monitor patients with these disorders, but this may give a false sense of security as patients may develop marked encephalopathy before blood glucose concentrations fall: treatment must be started before this.

Conclusions

The use of a well planned emergency regimen will not only help prevent episodes of metabolic decompensation, but will reduce hospital admissions and improve the parents' self confidence. The policy of encouraging the family to bring the unwell child to hospital every time is intended to be supportive and may initially be necessary, but it may add to the burden of care. The correct balance needs to be found between overzealous intervention and the risk of complications. Furthermore, the needs of each child and their family must be judged carefully and the instructions adjusted to their own individual requirements.

We would like to thank Dr Peter Clayton and Dr Margaret Lawson for their constructive criticism of the manuscript.

Note References about the inborn errors have, in general, only been given where the statement is not substantiated in Scriver *et al*[1]

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Appendix *Manufactured products used in maple syrup urine disease (MSUD) and urea cycle disorders (UCD)*

Product	*Amino acids (g/100 g)*	*Energy (kcal/100 g[*])*	*Carbohydrate (g/100 g)*	*Fat (g/100 g)*	*Vitamins and minerals*	*Comments*
(A) Maple syrup urine disease: these products contain all amino acids except the branched chain ones, leucine, isoleucine, and valine						
Analog MSUD (1)	15·5	462	54	23	Full range	Infant formula
Maxamaid MSUD (1)	30	300	51	<0·5	Full range	Suitable from 2 years of age, good solubility
Maxamum MSUD (1)	47	290	34	<0·5	Full range	Suitable from 8 years of age, good solubility
MSUD Aid (1)	96	320	Nil	Nil	Limited range	Low solubility (not suitable for continuous feeds)
MSUD 1 (2)	49	280	29 (sucrose)	Nil	Full range	For infants high sucrose content, requires fat to be added
MSUD 2 (2)	65	310	22 (sucrose)	Nil	Full range	For children
MSUD diet powder (3)	12	483	63	20	Full range	Infant formula
(B) Urea cycle disorders. these products contain a mixture of essential and non-essential amino acids						
Dialamine (1)	30	360	62 (54 g sucrose)	Nil	Limited range, low content	Orange flavoured, high sucrose content
UCD 1 (2)	68	260	8·0 (sucrose)	Nil	Full range	For infants requires carbohydrate and fat to be added
UCD 2 (2)	81	290	6·0 (sucrose)	Nil	Full range	For children

Manufacturer: (1) Scientific Hospital Supplies (SHS), Liverpool, (2) Milupa, Hillingdon, Middlesex, (3) Mead Johnson Nutritionals, Hounslow, Middlesex In the UK. Only the SHS products have been approved by the Advisory Committee Borderline Substances and can be prescribed on an FP10.

[*] 1 kcal=4·18 kJ.

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TYPES OF PSYCHIATRIC TREATMENT

Treatment of delinquents

Carol Sheldrick

This is the tenth of a series of articles on treatment of child psychiatric disorders.

Definition

As West points out delinquency is a sociolegal category.[1] The definition of a juvenile delinquent, in the UK at least, is a young person between the age of 10 (the age of 'criminal responsibility') and 17 years who has been prosecuted and found guilty of an offence that would be classified as a 'crime' if committed by an adult. These offences normally result in the opening of a criminal record file at Scotland Yard but do not include more minor drunk and disorderly, common assault, and motoring offences.

The size of the problem

Research findings are consistent in showing that the majority of young people (particularly boys) have committed delinquent acts at some time. Not all boys appear in court, but self report studies do pick out many of the boys with official records and the higher the score on a schedule of self reported offences, the greater the likelihood of the young person having an official conviction record.[2–4] Farrington,[5] using data from the Cambridge study, a longitudinal study of 400 boys living in inner London and selected randomly from six adjacent primary schools[4 6–8] showed that up to the age of 32, over one third were convicted of criminal offences. The peak age for the number of offenders and the number of offences was 17, but approximately equal numbers of offences were committed by males as juveniles (age 10–16), as young adults (age 17–20), and as adults (21–32). The men who were first convicted at the earliest ages tended to become the most persistent offenders and committed large numbers of offences at high rates over long time periods. Despite this, earlier work by West, showed that only about one quarter of adolescent offenders continued to offend into their twenties.[7]

Much less research has been carried out on females but figures quoted by Farrington suggested that the ratio of males to females acquiring a criminal record was approximately 3·5–4·5:1.[9]

Implications for management

It is clear from this research that a certain amount of law breaking is the norm, particularly for males, and does not necessarily imply any significant degree of personal maladjustment. Many youths only appear in court once and only a small proportion show a persistent pattern of delinquency. While it may seem appropriate to intervene as early as possible in the lives of delinquents research suggests otherwise.

The dangers of intervention

THE JUDICIAL PROCESS

There are differing theories about the judicial response to delinquency. The work of Farrington *et al* has shown that the first appearance in court tends to be followed by an increase in delinquent activities, as well as increases in hostile attitudes towards the police, aggressive attitudes and behaviour.[10] This study suggests that a first court appearance (and public labelling) has a deleterious effect, and probably more so if the consequences are trivial. A study by McCord suggests otherwise, however.[11]

In Britain we lock up a higher proportion of our population than most other Western European countries. At one time it was hoped that institutional treatments would be therapeutic and reformative in their effects. Unfortunately this has not proved to be so and some studies from America show that non-custodial approaches do better than institutional ones.[12 13] McCord, in the study referred to above, showed that incarcerated boys do not do better with respect to recidivism than those receiving more lenient sentences.[11] In England there is no evidence that the borstal (now renamed the young offender) system is effective in influencing long term recidivism. Sixty four per cent of trainees released in 1972 were reconvicted within two years; the figure for boys under the age of 17 years was even higher, at 79%.[14]

It seems unlikely that institutional treatment, retraining, and punishment are effective in decreasing delinquency. It is even possible that there is a harmful effect because of the alienation, stigmatisation, and 'contamination' suffered by those who are incarcerated together with other offenders.

COMMUNITY BASED PROGRAMMES

Similar results would not have been anticipated from community based, non-punitive programmes. Unfortunately this is not so and one study by O'Donnell *et al* showed that non-delinquents had a worse outcome than controls, possibly because of delinquent peer group contamination.[15] An important study by McCord looked at the long term effects of a treatment programme for boys and their families based on a 30 year follow up of over 500 men, one half of whom had been randomly assigned to a treatment programme at the age of 5–13 years, for an

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average of five years.[16] Treatment consisted of counselling for the boy and his family, introduction to community programmes and summer camps, provision of medical and psychiatric assistance as well as tutoring in academic subjects. The treated group actually fared worse than the control group on such measures as criminal behaviour, death at a young age, stress related disease, alcoholism, serious mental illness, occupational status, and job satisfaction.

There have been more successful community based programmes developed, mostly in North America, and reviewed by Stumphauzer,[17] however.

Attempts at diversion

THE COURTS

It is clear from this research that diversion of young people from certain interventions, particularly those of the courts and the prison system, is desirable.

In Britain the Children and Young Persons Act 1969 was introduced in order to prevent children coming to court for criminal proceedings.[18] Before 1971 children could be given a warning if apprehended while committing an offence. This was an informal procedure, conducted at the discretion of the police officer and not recorded officially. The 1969 act gave statutory sanction for police cautioning as a means of diverting children from the courts. The caution is usually administered, with the consent of the child, parents and victim, in a formal way to emphasise the gravity of the situation. Sometimes the police undertake follow up supervision and guidance, or they may refer the child to the social service department on a voluntary basis.

In 1979, the year when the legislation was fully implemented, it was found that cautioning increased,[19] which led Farrington and Bennett to believe that this had produced a widening of the net, so that official cautions had tended to replace informal, unrecorded warnings, rather than being used in place of court appearances.[20]

The situation since then appears to have changed for the better, however. Richardson and Tutt,[21] using data from the Home Office,[22] point out there has been a 23·2% decrease in the number of 10–16 year olds in the population in England and Wales over the 10 years 1979–88. It has been found that over 55% fewer juveniles entered the formal court system during 1988 than did in 1979, a very dramatic diversion of young people away from the courts.

THE USE OF COURTS FOR CARE PROCEEDINGS AND INTERVENTION IN THE COMMUNITY

In England courts have basically two types of case to hear: care proceedings and criminal proceedings. Under the age of 10 years a child cannot be found guilty of a crime (except homicide) and between 10 and 14 years should not be prosecuted for a crime. This means that all those under the age of 14 years should come before the courts for care proceedings only. An additional safeguard is that the 1969 act,[18] replaced by the Children Act 1989,[23] sets out criteria for taking out care proceedings. Under the terms of the Children Act 1989, a care order may no longer be imposed as a sentence in criminal proceedings. However the fact that a child had committed an offence may indicate that he or she is suffering, or likely to suffer, significant harm, so that the local authority may apply for a care order in respect of that child.

THE USE OF SUPERVISION ORDERS

These orders were originally introduced in the Children and Young Persons Act 1969[18] as a means of dealing with offenders through an intermediate treatment programme (see below). They can now be linked to a number of disposals (Children Act[23] and Criminal Justice Act[24]). Supervision orders may still be made criminal proceedings, the statutory responsibility lying with the local social services or, in the case of older juveniles, with the probation service. The primary consideration is to 'advise, assist and befriend', and not to protect the public, though the supervisor can return the young person to court if the terms of the order are breached.

SUPERVISION ORDERS WITH A SUPERVISED ACTIVITY REQUIREMENT

The supervised activity requirement can be made by magistrates and social services have to accept it. Placements are usually drawn from the intermediate treatment scheme.

Intermediate treatment has been adopted since the white paper *Children in Trouble* was published by the Home Office.[25] The aim is to fill the gap between simple supervision and removal from home. It is designed to allow the child to remain in his home, but bring him into contact with a different environment, interests, and experiences that may be beneficial to him and enable him to share them with other children who have not been before the courts. Although intermediate treatment is usually community based, it can be provided in a residential facility for up to 90 days. As Cawson points out, the end of the 1970s saw two major developments in practice: 'intensive intermediate treatment' to provide a real alternative to removal from home, and the introduction of new methods for working with groups.[26] Nevertheless there is still substantial disagreement within social work as to the desirability of programmes that are an alternative to custody programmes, and many intermediate treatment programmes are still focused on non-offenders, or even exclude serious delinquents.

CUSTODIAL SENTENCING

We have a history, in Britain, of locking up large numbers of young people. The numbers dealt with in this way escalated dramatically during the 1960s and 1970s,[27] and particularly so immediately after the introduction of the Criminal Justice Act 1982.[28] These trends were seen for girls as well as boys.

The situation during the 1980s has changed for the better however. As has already been noted there has been a large increase in the numbers of young people diverted from the courts in Britain from 1979–89. The same trend has been mirrored by the numbers of young people receiving custodial sentences—that is, 7097 in 1979 and 2176 in 1988.[22]

It is of interest to note that similar changes have occurred within the child care system a great increase in the provision of secure accommodation having occurred in the 1970s, with a decline in its provision during the last decade.[29]

Is treatment of delinquency possible?

CAUSES OF OFFENDING

Numerous studies have shown that delinquency tends to be much more frequent in adolescents coming from certain kinds of family and social backgrounds. The most important variables associated with juvenile delinquency are: large family size, poverty, parental criminality, marital conflict, poor parental supervision, cruel, passive or neglecting attitudes, and erratic or harsh discipline[4 30 31] Farrington has shown that the childhood predictors of conviction up to the age of 32 can be grouped into six major conceptual categories: socioeconomic deprivation poor parental child rearing, family deviance, school problems, hyperactivity-impulsivity-attention deficit, and antisocial child behaviour. He suggests that the link between antisocial child behaviour[5] and offending probably reflects an underlying construct of antisocial personality, and goes on to suggest that the other five constructs are possible causes of offending.

IMPLICATIONS FOR TREATMENT

The implications for planning treatment from these considerations are considerable. Whatever the theoretical starting point it is generally agreed that there is no single cause of delinquency; the factors initiating delinquency are probably not the same as those maintaining it. It is unclear how the various factors interact, and most of those identified tend to be inter-related anyway. As discussed by Rutter and Giller it is difficult to know which possible cause to treat, particularly bearing in mind the gap between identifying a damaging influence and knowing how to mitigate or eliminate it.[32]

The work of Farrington suggests that potential offenders can be identified at an early age with a reasonable degree of accuracy and that, on the basis of current empirical evidence, the most helpful methods of reducing juvenile offending are through parental training and educational programmes.[5] Other possible interventions include giving more economic resources to poor families, providing juveniles with socially approved opportunities for excitement and risk taking, deterring offending through an increased probability and level of penalty (although this also has dangers), increasing the physical security or surveillance of potential targets, and encouraging resistance to antisocial peer pressures.

Who to target?

THE INDIVIDUAL AND THE FAMILY

A medical model of delinquency has been in vogue for many years. Within this model the major determinants of delinquent behaviour are regarded as being located within the individual, the maladjusted personality being the result of genetic inheritance or the product of early experiences and relationships, especially from within the family (see Bowlby[33]). While such a model might suggest a psychotherapeutic approach to the treatment of delinquents it has been found to be of value with only a relatively small number of anxious, introverted young people who are aware of their personal problems and who want help for them. In the past 20 years there has been a considerable increase in the application of behavioural treatment programmes for antisocial and aggressive behaviour. Yule has reviewed the most important of these techniques.[34]

The most extensive behavioural family intervention studies have been those undertaken by Patterson and his colleagues at the Oregon social learning centre.[35–37] Both aggressive children and delinquents have been treated using a behaviourally orientated parent training programme. Parents are helped to use positive, non-coercive methods of control; to interact more positively as a family; to monitor their children's activities better and to deal more decisively with deviant behaviour; to negotiate behavioural contracts with their children; and to develop improved social problem solving skills. The findings have shown that both aggression and stealing can be markedly reduced by this approach, but that the benefits are much shorter lived with the latter group. While this approach offers great promise, the published studies so far have been flawed by methodological difficulties. Kazdin *et al* are researching further the possible benefits of parent management training and cognitive-behavioural problem solving skills.[38 39]

An important development has been the establishment of residential group homes, closely integrated with the community and run on behavioural lines. The best example of this approach is provided by the achievement place studies.[40–44] The model provides a community based, family style, group home treatment programme for six to eight youths aged 12–15 years who are in danger of being institutionalised. The programme is administered by a couple referred to as teaching parents, who have had a year's professional training. The goal of the programme is to establish through reinforcement, modelling, and instruction the skills needed in the social, self care, academic, and prevocational areas that the youths have not acquired. There appears to be a significant reduction in offending during treatment, but no advantages at one year follow up.[45]

As Farrington states that if low intelligence and school problems are causes of offending, then any programme that leads to an increase in school success should lead to a decrease in offending.[5] He quotes the Perry preschool project carried out in Michigan by Schweinhart and Weikart.[46] This 'Head Start' programme and a later follow up study of this group by Berrueta-Clement *et al*[47] suggest great promise but requires replication.

THE RESIDENTIAL ESTABLISHMENT

Delinquent children who repeatedly come to the attention of the authorities tend, in this country at least, to end up in some form of residential care and much Home Office research has been directed towards evaluating and comparing such institutions.

Cross institutional designs have been used to look at the large differences that exist between institutions in the behaviour shown by similar types of residents while they are in their care. The first Home Office cross institutional study was designed and carried out by Sinclair.[48 49] The study was concerned to examine the probation hostel system, where it was found that the proportions of boys leaving the hostels prematurely as a result of absconding or further offending ranged from 14% to 78%. Sinclair found that certain qualities of the staff, in particular the wardens, were important. By using the Jesness staff attitudes questionnaires it was found that wardens with the lowest rate of premature leaving were those who ran a strictly disciplined hostel, but who also expressed warmth towards the boys and were in agreement with their wives about how the hostel should be run.[50] Those who were harsh, emotionally distant, lax, permissive, or who disagreed with their wives about hostel policy tended to have high drop-out rates from their hostels.

Many young people are placed in community homes with education on the premises (CH(E)s). (Before the 1969 Children and Young Persons Act[18] these were known as approved schools.) Studies by Millham *et al*[51] and Sinclair and Clarke[52] have shown that successful schools are dependent on qualities of staff and combine a harmonious atmosphere, good staff-pupil relationships, kindness, consistency, firmness, with high expectations, a high level of activities, and vocational training. Dunlop's more detailed study of eight CH(E)s, catering for boys aged 13–15 on admission, showed that schools that appeared to lay emphasis on trade training and on mature and responsible behaviour had lower rates of both absconding and other forms of misbehaviour during admission as well as having marginally, though significantly, better reconviction rates.[53]

In their comparison of 12 inner London secondary schools Rutter *et al* showed that delinquency rates were probably affected by school factors such as appropriately high expectations, good group management, effective feedback to the children with ample use of praise, the setting of good models of behaviour by teachers, pleasant working conditions, and giving pupils positions of trust and responsibility.[54]

THE THERAPIST

Research into institutions and the use of specific techniques has led to an increasing awareness of the importance of therapist qualities. As early as 1967, Truax and Carkhuff's work with adults being treated with Rogerian counselling emphasised that effective counsellors were characterised by genuineness, empathy, and non-possessive warmth.[55] Subsequent work has shown a great deal of inconsistency in the effects of these therapist variables (see Mitchell *et al*[56]) and other studies have suggested that different qualities are important. Alexander *et al* examined therapist variables in relation to interventions with families of delinquents.[57] They found that 60% of the outcome variance in treated cases was accounted for by structuring and relationship skills (these latter being composed of several behaviourally defined categories including affection, warmth and humour). Kolvin *et al* found substantial differences between therapists in their effectiveness in treating children, but that the important qualities were extroversion, assertiveness, and openness.[58] Clearly, research indicates that therapist qualities are important, but further studies are required in order to establish which are the most important ones and whether or not they can be taught.

Is there a medical role in the treatment of delinquency?

ASSESSMENT OF DELINQUENTS

While delinquents have many features in common, it has often been observed that some patterns of delinquency overlap with aggression, emotional disturbance, poor peer relationships, hyperactivity, and attentional deficits. These problems may well require assessment and treatment in their own right, which can best be provided by a multidisciplinary team based in a child psychiatry department or child guidance clinic. These teams are usually headed by a medically qualified practitioner, but the medical role in the assessment and treatment of delinquency is probably a limited one.

Counselling and psychotherapy, based on the establishment of a personal relationship, have rarely proved successful except for a small minority of rather anxious, introverted young people who are aware of their personal problems and want help with them. Overt neurological disorder or severe psychiatric abnormality are met with only occasionally in adolescent offenders. Those with hyperactivity and attentional deficits may benefit from medication and those with emotional disturbance from individual or family psychotherapy. However, the numbers that can be helped in these ways are few. For the majority, treatment aims are probably best directed towards improving the educational, vocational, practical, and social skills of the individual and a problem oriented approach to assessment and treatment of young offenders promises to be the most effective. Such an approach has been described by Stumphauzer.[17]

REQUESTS FOR PSYCHIATRIC COURT REPORTS

Despite the fact that the medical role in the assessment and treatment of delinquency is limited, psychiatrists are often asked to prepare reports on young offenders for the court. There are a number of different issues on which they are asked to advise. The first, and cost obvious, is to comment on the presence (or absence) of mental illness. Signs which might suggest these are reports of self damage, extreme changes of mood, and recent changes in personality. A history of solvent or drug abuse may also give cause for concern. Aspects of the background history, in the absence of any obvious symptoms, such as a previous history of mental illness in the family, may also lead to the request for a psychiatric opinion. A psychiatrist may also be involved in the assessment and management of some developmental delays, physical conditions and illnesses, especially if there is an emotional component. The investigations for speech disorder, enuresis, and epilepsy provide examples: the hyperkinetic syndrome of childhood deserves special investigation and treatment. A request may be made for an adolescent to be seen alone, or with his family, and in this context it may be possible for a psychiatrist to express a view on the personality and emotional development of the young person, other members of the family, or on the functioning of the family as a whole.

Other indications for assessment are unusual or bizarre behaviour either reported in the past, possibly at the time of an offence, or even witnessed in court during a hearing. Inexplicable, repetitive offending, sexual deviancy and dangerous behaviour, such as fire setting and serious assault against another person may lead to a psychiatric referral.

As with adults, a specific request for assessment of dangerousness, fitness to plead, diminished responsibility, and treatability within the resources of the health service may be requested of psychiatrists. In addition they are often asked to advise on, or support recommendations for, placements within the child care system, and often have an important role in consulting to establishments within that system.

Summary

The medical role in the treatment of delinquency is a limited one. There is conflicting evidence as to whether treatment aims should be directed towards the individual, to the family, the institution, or the therapist. Nevertheless there seems to be a consensus of opinion that short term, focused therapies aimed at improving educational, vocational and social skills, possibly from a preschool age, are the most effective. Any treatment gains achieved while in residential care appear to be short lived. It therefore seems that this should be reserved for those individuals who commit repeated, violent crimes and for those from very damaging family backgrounds who repeatedly abscond or absent themselves from community based programmes.

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CURRENT TOPIC

Should we use dexamethasone in meningitis?

The Meningitis Working Party[1] of the British Paediatric Immunology and Infectious Diseases Group

Meningitis in Britain is still a common and serious disease. Each year 2000 cases are reported to the Communicable Disease Surveillance Centre (CDSC), and possibly as many again go unreported. Altogether 70% of cases are in children, and the overall mortality is 10%.[1] This means that more children die each year of meningitis than of either liver disease or kidney disease.[2]

Although the prognosis following bacterial meningitis improved dramatically after the introduction of antibiotics, there has been no major decline in the morbidity or mortality for three decades. This is despite a range of excellent antibiotics which are very effective in destroying the causative organisms. Meningitis is the commonest cause of acquired postnatal sensorineural deafness in childhood,[3] and also produces epilepsy and neurological damage as sequelae.[4 5]

In the past decade evidence has accumulated from both cellular and animal studies to suggest that much of the cerebral damage is the direct result of activation of host inflammatory pathways rather than a direct consequence of the invading organism.[6] Steroids in vitro block the release of inflammatory cytokines from macrophages and other host cells,[7 8] and in vivo animal experiments have shown that both the inflammatory response and the resulting organ damage occurring in meningitis can be reduced by steroids.[9] This has led to the suggestion that anti-inflammatory treatment may be helpful in human disease. A number of clinical trials have now been undertaken which suggest a beneficial effect from steroids, and a heated debate has developed as to whether steroids should now become a routine part of the treatment of meningitis.

How strong is the evidence?

In vitro studies

There is now good evidence that the inflammatory cascade induced by bacterial products such as endotoxin is initiated by cytokines, particularly tumour necrosis factor-α (TNF-α)[10] and interleukin-1β (IL-1β).[11] Synthesis and release of these cytokines can be suppressed by pretreatment of cultured cells in vitro with dexamethasone.[7 8]

Animal studies

The inflammatory response occurring in the cerebrospinal fluid of rabbits after intracisternal injection of either bacterial products such as endotoxin or of live *Haemophilus influenzae* organisms can be blocked by dexamethasone. This is effective when administered before or with (but not after) an antibiotic.[9] TNF-α and IL-1β concentrations in the cerebrospinal fluid are reduced concomitantly. Similar effects have been shown in experimental pneumococcal meningitis,[12] in which intracranial hypertension, brain water, and cerebrospinal fluid lactate concentrations can be reduced by steroids. In addition, the inflammatory response induced by intracisternal administration of recombinant TNF-α or IL-1β to rabbits is similarly decreased by prior treatment with dexamethasone.[13]

Clinical studies

HAEMOPHILUS INFLUENZAE

Based on this and other evidence, several clinical trials were established, initially by workers in Dallas, studying bacterial meningitis in infants and children. Lebel *et al* studied 200 children on two antibiotic regimens for bacterial meningitis.[14] Most had infection with *H influenzae*. They were randomised to receive either dexamethasone 0·15 mg/kg or placebo at the onset of treatment and then six hourly for four days. These trials suggested that the children treated with steroids had a more rapid correction of abnormal cerebrospinal fluid parameters (glucose, lactate, protein), a shorter duration of fever, and significantly less long term hearing loss than the placebo group. Particularly impressive was the reduction in sensorineural deafness (3·3% in the steroid treated group compared with 15·5% in the placebo group). Critics were quick to point out that the overall death rate in this study was very low (only one patient died) and that the 15·5% incidence of sensorineural hearing loss in the control group was much higher than that found in other studies. (Pomeroy *et al* found an overall incidence of sensorineural hearing loss of 10% in their patients,[15] and other groups have found the incidence to be even lower.) Despite these criticisms, the improvement in morbidity appeared striking.

A further study from the same centre on only 60 patients failed to detect a statistically significant difference between steroid treated and control groups with regard to hearing loss,

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although the steroid treated group again showed more rapid normalisation of cerebrospinal fluid abnormalities.[16] Since then, Odio, from Puerto Rico working in conjunction with the Dallas group, again failed to find a statistically significant reduction in deafness in her steroid treated group,[17] but showed an overall reduction in the incidence of 'neurological complications' compared with a placebo group.

Eighteen months ago, a meta-analysis of all published trials of steroids in bacterial meningitis was performed.[18] The results showed that steroids had not reduced the overall risk of death or neurological abnormality at hospital discharge or follow up examination. When many of the variables between studies were eliminated by analysing the only five studies performed primarily in children, there was still no significant difference in this subset. However, restricting the analysis to the three (then) most recent studies, all of which came from the same unit in Dallas, evidence was found that *in haemophilus infections alone*, dexamethasone reduced the risk of bilateral moderate or more severe hearing loss (although a statistically significant benefit was only found in one of these three studies).

Can we apply these results to British practice directly?

The vast majority of cases of childhood meningitis seen in North America in the 1980s were due to *H influenzae*, and the above trials concentrated on this organism. Since these studies, effective haemophilus vaccines have been introduced in many countries, including the USA, and will be in general use in Britain by the end of 1992. Haemophilus meningitis is likely to become much less common in this country within a few years.

So what about the other organisms?

MENINGOCOCCUS

Meningococcal meningitis is at least as common as haemophilus in Europe, and will become relatively more important with the decline of haemophilus disease. However, few data are available for the effect of steroids in this condition.

In a controlled trial of steroids Girgis *et al* studied 429 adults and children with bacterial meningitis in Cairo, Egypt.[19] Of these 267 were due to meningococcal infection. Despite this large number there was no evidence that the steroid treated group fared any better than those given antibiotics alone. The mortality and incidence of serious sequelae was equal in both groups. The authors suggested that this may have been because the damage had already occurred before the patient reached hospital. There is some experimental and clinical support for the suggestion that hearing loss (for example) occurs very early in bacterial meningitis.[20 21] Unfortunately it is difficult to extrapolate from the results of this trial to our own clinical management. These Egyptian patients were extremely sick (60% were comatose on admission), and neither the occurrence of subtle neurological defects nor the incidence of possible side effects was carefully monitored. In addition the pathophysiological changes in meningococcal meningitis may not be identical to those in haemophilus meningitis. The clinical picture differs (meningococcal disease is more frequently associated with septicaemia and a purpuric rash for example), and other as yet undefined factors may have a role in meningococcal disease.

There is no evidence available to assess the role of steroids in meningococcal meningitis with septicaemia and septic shock. In other forms of septic shock there is little evidence that steroids are beneficial (even when given early), and they may possibly be harmful.[22] We would therefore recommend caution in using steroids in children with meningococcal meningitis with associated septic shock until more evidence is available.

PNEUMOCOCCUS

What about pneumococcal meningitis? Although in Britain this is the least common of the three major agents causing bacterial meningitis in infants and children, the morbidity and mortality is higher than for either haemophilus or meningococcal infections. There is little published evidence that steroids may be of value here: the Egyptian study by Girgis and colleagues quoted above found a reduction in the mortality and morbidity of patients with pneumococcal meningitis receiving steroids,[19] and a small retrospective study from Dallas suggested that fewer steroid treated patients had an adverse neurological outcome.[23]

Several other studies have been initiated since 1989, both in North America and in Europe; to our knowledge none of these have yet produced statistically significant results. No evidence is currently available for a role for steroids in neonatal meningitis, although trials are in progress.

Complications of steroids

Do the complications of steroid treatment outweigh its advantages?

Two patients who received steroids in the original Dallas studies had sufficiently severe gastrointestinal bleeding to need transfusion, and two other children had detectable 'occult blood in their stools.[14] Information on the complications of steroids from many of the other published studies are incomplete, and the overall morbidity of adjunct steroid treatment is, in our opinion, still unclear. An experimental study in rats has suggested that steroids potentiate ischaemic damage to neurons,[24] with obvious implications for clinical management.

The use of dexamethasone may delay sterilisation of the cerebrospinal fluid. Although this was noted in only one patient in the Dallas studies, it remains a clinical concern for many, and further data from other centres would be reassuring.

As all the evidence suggests that steroid treatment is only beneficial if given very early (preferably even before the antibiotic) a number of children with viral meningitis will be treated with steroids for short periods (probably up to 48 hours). No adverse effects from the steroid treatment have yet been reported, but very few children in this group have been studied, and more information is still required.

Rationale for steroid treatment

The rationale for steroid treatment is dependent on the concept that the damage is primarily due to the host inflammatory response rather than the direct effect of a toxin produced by the organism itself. Is this necessarily the case? There is evidence that it is true in *H influenzae* meningitis,[25] in which the pathogenic material is considered to be lipopolysaccharide of the outer cell membrane (LPS, endotoxin), a substance that primarily provokes the release of host cytokines but is itself largely non-toxic to many mammalian cells. In pneumococcal meningitis, cell wall lipoteichoic acid may play the same part as Gram negative LPS,[26] but here there is some evidence that other substances such as pneumolysin (a pneumococcal exotoxin) may also be involved. Pneumolysin can directly damage tissues, probably by producing pores in cell membranes.[27] If this is part of the mechanism of pneumococcal damage, pneumococcal disease might not be as steroid responsive as haemophilus meningitis. Few studies have been performed on the mechanism of tissue damage in meningococcal meningitis. Although meningococcus like haemophilus, is a Gram negative organism containing LPS in its outer cell membrane there is no certainty that it produces tissue damage in the same way; indeed the very different clinical patterns of disease produced by the two organisms suggest that their mechanisms of toxicity may differ in important ways.

There is thus little adequate data from any North American study to demonstrate a convincing benefit resulting from dexamethasone administration in meningitis due to any organism other than haemophilus. More studies are called for. There are still no published studies from Europe, where the incidence of deafness and other complications may be less than in the populations studied by the Dallas group, and where antibiotic use and clinical practice is often different.

After reviewing the evidence, the Committee on Infectious Diseases of the American Academy of Pediatrics concluded that 'Dexamethasone therapy probably reduces the likelihood of deafness after *H influenzae* meningitis . . . The utility of dexamethasone in treatment of pneumococcal or meningoccal meningitis is not yet known'.[28]

Conclusion

In conclusion then, it seems probable that children with haemophilus meningitis may benefit from the use of early adjunct treatment with dexamethasone, particularly in the reduction of deafness. Almost all the evidence for this comes from a single unit in North America, and different parameters have shown benefit in different trials. The advantages of steroid treatment here probably outweigh the disadvantages. The case for pneumococcal meningitis is minimal, based in a retrospective study from Dallas and on a subgroup of a Cairo study performed in a mixed group of adults and children. Very limited information is available for meningococcal meningitis. What evidence there is suggests steroids may not help. As there are well established risks associated with steroid administration to septic patients, especially those in shock, there is an urgent need for further studies to confirm or refute this potentially major change in our management of a widely and justly feared infection.

How easy would these be?

It would be necessary to recruit very large numbers of patients and controls (many hundreds) into a placebo controlled trial of dexamethasone designed to confirm or refute a 50% reduction of moderate/severe deafness in bacterial meningitis. The patients would need careful monitoring and audiological follow up over a prolonged period. We may be approaching the point at which this type of controlled study can no longer easily be performed in Britain alone.

A European multicentre trial may be the answer.

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That disease again

There is no doubt that Kawasaki disease (in this journal we refer to Kawasaki disease and Down's syndrome; don't ask me why though I note that Tomisaku Kawasaki himself puts his name to the unapostrophised form) has a certain fascination for paediatricians. Is it the unusual clinical features, the diagnostic challenge, the rarity of coronary disease in paediatrics, or simply the exotic name which catches the imagination? The subject was well covered in the December 1991 issue of the *Archives* and I would hesitate to raise it again were it not for the publication in *Pediatrics* of data about the cardiac sequelae of the disease from a very large survey in Japan by Yosikazu Nakamura and several colleagues including Dr Kawasaki (*Pediatrics* 1991;**88**:1144–7).

Between July 1982 and December 1988 no fewer than 46 864 cases of Kawasaki disease were reported in Japan. Sixteen per cent of them had cardiac sequelae at least one month after the onset (that is 'the presence of aneurysms including dilatation or stenosis of coronary artery, myocardial infarction, or valvar lesions'). Heart disease was about one and a half times as common in boys as in girls. During the 6·5 year period there was a modest decrease in the proportion of patients developing heart disease (from 16·5% to 14·2%) and a large increase in the proportion receiving gammaglobulin (from 2·5% to 54·8%). Those with cardiac sequelae had more commonly been treated with intravenous gammaglobulin probably because the treatment was given to those with serious disease. It has previously been reported that the mortality from the disease fell from 2% in 1967 to 0·1% in 1986.

This study adds to the epidemiological data about Kawasaki disease and its sequelae but provides no evidence to support or refute the use of immunoglobulin.

ARCHIVIST

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CURRENT TOPIC

African children in Britain

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Historical background

African children have been living in Britain since the 16th century. Brought by slave traders they were advertised, auctioned, and sold as servants in Bristol, Liverpool, and London. They often worked in aristocratic households and are portrayed in groups of the period by Zoffany and Reynolds.[1]

After the abolition of the slave trade Britain's black community divided and intermarried. From the mid 19th century small numbers of West Africans, mainly unaccompanied men came to Britain to study law, theology, and medicine at the behest of parents, missionaries, and philanthropists. In 1950 there were 90 African students in Britain, towards the end of the 1960s as independence became a reality, the numbers had increased tenfold.[2]

A Colonial Office report of 1955 recognised the isolation and discrimination experienced by students and actively encouraged accompanying families.[3] The difficulties they experienced are well described in Buchi Emecheta's semiautobiographical novel *Second Class Citizen*.[4] The period of stay in Britain often exceeded five years, but most students eventually returned home to significant positions in government service.

The optimism and high expectations that followed independence have not always been fulfilled. Most African countries face major debt crises for the foreseeable future. Civil wars, political instability, population pressure, and drought have exacerbated their difficulties and resulted in a diaspora of the African urban middle class, often to countries with old established links, but also to the Middle East and southern Africa.

Population statistics

The Labour Force Survey (1988) estimated the settled African population in Britain was about 122 000. This represented an increase of about 30% since 1981.[5] Since 1988 acceptances for settlement in Britain to African nationals have doubled to around 8000 per annum. In 1990 African children accounted for 1350 of these acceptances. In the same year, leave of entry was granted to 113 000 Nigerians, 38 700 Ghanaians, and 10 800 Sierra Leoneans.[6]

Applications for refugee status and asylum in Britain have increased tenfold over the past three years to an estimated total of 50 000 for 1991, with a substantial majority of applicants coming from Somalia, Ethiopia, and Uganda.[7] Recent applicants have included unaccompanied children.

The Labour Force Survey of 1986 identified 71% of Britain's African population as living in metropolitan areas. London was home for 81% of the total,[8] and other cities with significant African populations included Birmingham and Liverpool. In 1987 African children represented 4·7% of the total state school population in London. The highest proportions of African schoolchildren were in the Boroughs of Hackney, Lambeth, Southwark, and Wandsworth.[9]

The number of live births in the UK to mothers born in Africa has increased from 3593 in 1985 to 4721 in 1989, an increase of 35% over four years.[10 11]

Studies relating to a neonatal haemoglobinopathy screening programme in a south London health authority identified the proportion of births to mothers born in Africa as rising from 6·1% in 1981 to 14·5% in 1989, the total number of births per year remaining constant (unpublished data interim report on Camberwell neonatal haemoglobinopathies screening programme 1990).[12]

Regretably the methods of collection of ethnicity data in medical and sociological studies are not always clear or consistent. Information relating to African children and families has often been aggregated into the simplistic categorisation of 'Afro-Caribbean' masking important differences within the group and making interpretation of findings difficult.

Social circumstances

African families living in Britain share many of the problems faced by all families living in inner city and urban areas, but they differ in their expectations, aspirations, and supporting social networks. Recent editions of *African Women*, a development journal published by African women in Britain, have drawn attention to some of the perceived difficulties of the African Community.[13]

The expectation of a recently arrived refugee family is as a safe haven for the vulnerable family members during the period of war or repression in their home countries. Most want to return, preferably with new skills to offer to their society. The most recently arrived refugee families are mainly from the Horn of Africa, but also include asylum seekers from Kenya, Angola, Sudan, and Zaire. Families are often fragmented with husbands and older sons left behind, their whereabouts unknown. English language skills are initially limited and trained interpreters scarce, limiting access to benefit rights, health care, and training programmes. Accommodation is frequently in homeless family units or 'bed and breakfast' establishments.

The expectations of a family from West Africa were previously educational but are now primarily economic. The per capita income in Nigeria has fallen from $1000 year in 1983 to less than $250 in 1990 and employment opportunities have disappeared. Employment opportunites in Britain have been reduced by the current recession forcing professionally qualified Africans into low paid casual work with catering, cleaning, and security firms. The financial pressure to remit money home to the extended family often forces both parents to work.

The distinctions between being a visitor, a student, an economic migrant, and an asylum seeker are often blurred. The rapid changes in Africa can mean that today's visitor or student becomes tomorrow's asylum seeker. Economic pressures convert today's *bona fide* student to tomorrow's economic migrant; political instability changes today's president to tomorrow's refugee.

Childcare

Childcare presents a problem for all working parents, particularly for the West African mother used to family support. Local authority day nursery places and college creche places are limited and play groups and nursery classes are rarely full time. Private nurseries are prohibitively expensive and registered child minders charge over £50–60 a week. After paying overheads there is little left from a casual worker's salary. One of the child care options is a well organised partnership with the child's father which can work successfully where one partner is a student or works a shift system.[14] Another option is that the child/children are fostered in West Africa by a member of the extended family, often grandmother. This is a culturally accepted practice, but is unattractive at times of economic hardship in Africa. A third alternative is a private fostering arrangement in Britain. The costs are similar to those of a daily child minder and allow the parents additional flexibility to work long unsocial hours and increase their earning capacity.

The practice appears to have begun in the mid 1950s at the time of the Colonial Office policy change and is well established in parts of Suffolk, Hampshire, Avon, mid Kent, and Sussex. It is estimated that there are between 6000–9000 privately fostered children in Britain at present, the majority of west African parentage. In a study of 81 children of African born parents entering south London primary schools between 1988–90, 29 (37%) had been fostered in Africa or Britain for varying periods before school entry (A Nesbitt, unpublished MSc thesis, 1990 University of London).

Some foster placements were and are successful but the quality of others has been questioned. The Commonwealth Student's Children's Society and latterly the Save the Children Fund's African Family Advisory Service (AFAS) have tried to contain, monitor, and support private foster placements. Concerns identified by AFAS have included minimal knowledge of the children's background, culture, and medical history by the foster parents, limited information about the children's natural parents, some of whom were known to have returned to West Africa (usually Nigeria), children being passed between foster families, understimulation and educational underachievement, inadequate use of medical services by foster parents, and confusions in the children about their racial identity.[15]

AFAS was subsequently contracted by the Department of Health to advise of the draft regulations on private fostering in the 1989 Children Act. Under the regulations now in force local authorities are required to develop systems of notification from foster parents, birth parents and third parties, including health and education workers. In the guidelines the importance of delegating responsibilty of consent for medical treatment is stressed, as is the transfer of medical and parent held records and adequate information to foster parents about the child's medical history.[16] While the regulations and guidelines offer a model of good practice, it remains to be seen whether the resources and personnel needed to implement it are in place.

Some West African families become foster parents themselves, fostering in Britain older children from the extended family in Africa, continuing a long established traditional practice. This group of children appear particularly vulnerable as they try to adapt simultaneously to a new country, family, and educational system.

Drug related offences

The economic pressure in West Africa have led to increasing numbers of Africans, particularly Nigerians, becoming involved in the importation of drugs. There are at present approximately 300 West African women in British prisons serving sentences between three and 12 years many for drug trafficking offences.[17] A significant number of these women have children either in Britain or in West Africa. Children in Britain at the time of their mother's arrest are usually placed in local authority foster care, with attempts being made to continue mother-child contact by prison visiting schemes. At the end of the sentence mother and child are usually deported immediately. Nigeria's Decree 33 enacted in October 1990 and yet to be tested indicates that convictions for drugs offences overseas may result in a further prison sentence in Nigeria. The African community in Britain has been active in improving welfare services for African prisoners and their dependants.

African communities in Britain face the task of adapting to a new country in its own economic recession, at the same time shouldering responsibility and anxieties for their families in Africa.

Health needs

ANTENATAL AND NEONATAL SERVICES

The infant mortality rate for children born in the UK of African born mothers (excluding East Africa) was 11·2 per thousand in 1989 compared with an overall rate of 8·3 per thousand. The neonatal mortality rate for babies of African born mothers for 1989 was 7·4 per thousand compared with 4·7 per thousand for babies of UK born mothers.[11] However, the aggregated postneonatal mortality rate for babies of African born mothers (1982–5) was lower than that of babies of UK born mothers, with lower mortality rates for diseases of respiratory system and sudden infant death.[18] The stillbirth rates to African born mothers has increased from 6·6 to 7·8 per thousand over the 1985–9 period. The overall stillbirth rate in 1989 was 4·7 per thousand.[10 11]

Birthweight distribution for infants of African born mothers over the period 1982–5 was similar to that for infants of UK born mothers.[18] Black North American infants of low birth weight have been shown in a number of studies to have lower neonatal mortality rates from respiratory distress syndrome.[19 20] A study from south east London, which compared 'British', 'West Indian', and 'African' births found no significant difference in perinatal mortality among very low and low birthweight babies.[21]

The raised stillbirth and perinatal mortality rates in babies of African born mothers have implications for antenatal and special care infant services. A tendency for 'late booking' by African (and Asian mothers) in a south London antenatal clinic has been recorded.[22]

HAEMOGLOBINOPATHY SERVICES

Carrier rates for haemoglobinopathies in parts of Africa are high. In western Nigeria there is a 25% carrier rate for haemoglobin S, with a 2·5% incidence rate of sickle cell disease. Awareness of sickle cell disease in the African community is low. In contrast, the West Indian community has actively lobbied for the provision of improved services and health education programmes. African children now represent the largest user group in a number of the established sickle cell centres in Britain. In 1985, the Runnymede Trust Survey discussed the patchy and *ad hoc* nature of sickle cell anaemia services in Britain [23] Since then, funding for already limited neonatal screening programmes has been under threat and with the new NHS cross boundaries purchasing arrangements, high priority has not always been given to the provision of quality care for children with haemoglobinopathies. Ideally the facilities should include access to information, screening and counselling, as well as specialist paediatric input.

HEPATITIS B IMMUNISATION PROGRAMMES

The high prevalence rates of chronic carriage of hepatitis B surface antigen in African countries results in increased morbidity from liver disease and a raised incidence of hepatocellular carcinoma. Carrier rates in African women are probably up to 30%, with vertical transmission from mother to baby being closely linked to the mother's e antigen status. Perinatal vertical transmission rates in Africa and in the West Indian community in Britain are quoted as being between 0·3% to 5%.[24–26]

Policies for neonatal hepatitis immunisation in Britain at present vary. Some districts screen all women antenatally, immunising babies of e antigen positive mothers, others have a selective screening programme, yet other districts are now immunising all infants at birth. Maintaining high uptake rates for the second and third doses of vaccine is difficult as parents have often been poorly prepared antenatally about the reasons for immunisation. The long term international solution is the incorporation of an affordable vaccine into infant immunisation schedules; in Britain in the short term policies need to be rationalised.

SERVICES FOR HIV POSITIVE FAMILIES AND CHILDREN

The high prevalence rates of seropositivity to HIV in parts of Central Africa are well documented. Two London departments of genitourinary medicine have reported increasing numbers of HIV positive adults from Africa, particularly Uganda.[27 28] A 2% seropositivity prevalence rate is reported among African women attending a south London antenatal clinic.[22] Small but in service terms significant numbers of African children and adults living in London have developed full blown AIDS. Existing services have not been geared to the needs of African women and children living in social and cultural isolation. Medical management is at present based in major centres, but local support systems are developing.

BCG IMMUNISATIONS

BCG immunisation policies for African children in Britain may need to be reviewed. The incidence rate of tuberculosis in Somalia was rising before the outbreak of civil war[29] and notification rates in many African countries are high, with an increase in HIV related tuberculosis being reported world wide. At present the majority of children arriving from Africa have received a BCG immunisation neonatally, in some areas of Britain their siblings will also be immunised at birth, but in other areas immunisation will be at about the age of 13 years unless specifically requested by parents.

DEVELOPMENTAL DIFFICULTIES

Epidemiological data relating to developmental delay and disabilities in children of African born mothers in Britain is not available. There is a perception among educationalists and doctors that there may be an increased incidence of language and communication disorder, a pattern that has been noted in other immigrant communities (L Wing, unpublished data cited in Akinsola and Fryers).[30 31]

Again, there are service implications as well as the cross linguistic and cultural therapeutic challenge.

FEMALE AND MALE CIRCUMCISION

The term female genital mutilation is now being advocated to cover the different forms of female circumcision practised in Africa. 'Surgery' is radical in Sudan, Eritrea, and Somalia; less radical in Ethiopia and Sierra Leone. The procedure constitutes and offence in Britain under the Prohibition of Female Circumcision Act of 1985. Under the Children Act a Prohibited Steps Order can be made where necessary to prevent parents carrying out a particular act without the consent of the court—for example removing a child from Britain so that mutilation can be carried out abroad. FORWARD (the Foundation for Women's Health Research and Development) has led the campaign against female genital mutilation in Britain and has outlined action of strategies when proposed female genital mutilation in Britain is suspected.[14] They emphasise the importance of medical practitioners, nurses, midwives, social workers, and teachers being aware of the practice. Many African women in Britain speak openly of their own experiences and of their wish to protect their daughters from traditions and practices imposed by elderly female relatives.

Circumcision for many young African boys takes place in the newborn period. In West Africa, it is typically carried out by the midwife in hospital in the days immediately after delivery. In Britain hospital based circumcisions are hard to access and rabbinical services are frequently used. The Children Act guidelines for privately fostered children in Britain suggest that male circumcision should be carried out by a hospital or clinic based service and by a medical practitioner.[14]

CHILD ABUSE

Professionals in the field of child abuse and neglect in Britain and Africa have experienced little difficulty in reaching a consensus about what it constitutes as was demonstrated at a recent international conference (B Oloko, International Workshop on Child Abuse and Neglect, Lagos 1990). African communities, in general, condone physical punishment of the naughty older child, with extended family members controlling this effectively if it is excessive. In Britain, when the African nuclear family is under stress, physical punishment can get out of hand, leading to the instigation of child abuse procedures. Child protection agencies, however, have little experience in working in partnership with African families and can easily alienate families with what is perceived as confrontational interference. Conversely agencies by recognising traditional child rearing practices and giving them undue weight can neglect the child's needs.

Conclusion

In today's world of upheaval and change, professionals working with children in Britain must be willing and interested in realising an international perspective on child welfare in their day to day practice. They need to be responsive to the rapidly changing needs of Britain's immigrant communities.

The 1989 Children Act has the expectation that the ethnic background of the child and family will be taken into account when working with priorities and decision making. In December, 1991, the UK ratified the United Nation's Convention on the Rights of the Child. Its articles state the right of all children to enjoy the highest attainable standards of health, access to facilities for the treatment of illness and rehabilitation to health. In addition it states that protection be offered to refugee children. This legislation and the intent of the convention should offer a firm foundation on which to build effective flexible health services for all ethnic communities. Ultimately this will depend on strong equal partnerships with community leaders and commitment to the ideal that all children deserve to achieve their potential and enjoy their childhood.

We thank our African friends and colleagues for help, advice, and constructive criticism

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Challenges for child health in Australia

R Kim Oates

In any current discussion of child health in Australia, the financial aspect is usually predominant. Governments tell us that there has been a 'blow-out' in health costs. This argument is not supported by the facts which show that health expenditure in Australia has merely kept up with inflation, remaining at between 7·5% and 8·1% of gross domestic product for the last 15 years. The blow-out in health costs is in fact similar to the blow-out in the cost of ball point pens and breakfast cereal. For child health the challenge is how to get an adequate share of the health budget and how to use it most appropriately.

Of course there are many other clinical challenges which confront Australian paediatricians. Relatively little impact has been made on the two biggest causes of death of children after the first month of life, the suddent infant death syndrome in the first year and accidents beyond the first year. Even up to 1 month of age, while there has been considerable progress in the intensive care of extremely low birthweight infants, there has been far less progress in preventing the premature births which lead to these problems. Other major health challenges for Australian paediatricians, in terms of size and seriousness, include better understanding and improved management of asthma, a reduction in the number of cases of child abuse and neglect, and providing care for the increasing number of children surviving, often into adult life, with chronic handicaps.

While none of these challenges have simple answers, the four headings in this paper: health costs; hospitals, their communities and health delivery; child health education; and a national child health policy, are relevant to progress in these areas.

Health costs

The cost of health in Australia is borne largely by the tax payer. Taxation funds Medicare (a scheme of universal health insurance which covers the costs of hospital care in the non-private sector and 85% of the 'common fee' for medical consultations and surgical procedures), the Pharmaceutical Benefits Scheme, and some government funded research. The federal government also funds the bulk of hospital running costs through grants to the states although the states determine the allocation of these funds to hospitals.

Assuming that there will be no increase in the health budget, the problem for child health is to measure the effectiveness of what we do so that health services for children are not disadvantaged when health resources are allocated. While it is true that children are our future and that promotion of good child health is likely to reduce future adult health costs, facts are needed to support this argument. For children's health services to mount an effective argument for an adequate share of the health budget, effective outcome measures must be developed. Effective outcome measures enable logical decisions to be made about which areas of child health care may be able to be given up if they are found to be of little value and which areas need to be enhanced and improved, while at the same time providing a way of establishing the effectiveness of the newly introduced technology.

In an attempt to measure the activity of hospitals, and to determine their funding, Australia is looking at the introduction of diagnostic related groups (DRGs) for hospitals. As DRGs use average length of stay as a measure of cost and as children's hospitals have long had emphasis on children being in hospital for the minimal time, there is a danger that DRGs may disadvantage children's hospitals. Because adults in hospital often have multiple problems, while most children usually have only one or two problems, the DRG loading given to children's conditions for complexity is lower. Further, the range and complexity of some paediatric problems was not allowed for in the initial DRG formulation, although a revised version is more acceptable. The Australian Association of Paediatric Teaching Centres is currently assessing how DRGs can be used so as not to disadvantage children's hospitals.

Another way of looking at outcome is to use quality adjusted life years (QALYS). Quality of adjusted life looks at physical functioning, the person's role in society, their relationship to society and their health, with these measures being adjusted for longevity. This allows a comparison to be made between outcome and expenditure for different diseases. It can be a powerful tool in arguing for increased paediatric funding as most children who survive medical and surgical problems do so with a good quality of life and long life expectancy in comparison with the results of treating many adult diseases. QALYS can also can be used to make value for money comparisons between different paediatric treatments such as comparing costs and value of school screening procedures, or even neonatal intensive care, with the cost and benefit of introducing *Haemophilus influenzae* immunisation.

The development of efficient outcome measures will improve the quality of care we

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provide. Health costs are partly determined by the fact that health providers, particularly hospitals, have done things in the same way for such a long time that it is comfortable to keep things the way they are. A squeeze on the health budget has certainly raised the discomfort level and has been necessary to encourage innovative, lateral thinking as to the most efficient ways of providing health care for children.

While a proportion of the health budget should be set aside for research into outcome measures, laboratory and clinical research is largely funded by the federal government through the National Health and Medical Research Council's peer reviewed, competitive grant process. Federal funds for health research have been increased by 8% per annum in real terms since 1989 with initiative in such areas as asthma, the health needs of disadvantaged groups, public health research and opportunities for training young researchers. However, research expenditure is only 1·5% of total health expenditure, whereas the internationally recommended level is 2%. For child health, the challenge is for paediatric researchers to compete effectively with the other, often more research oriented medical disciplines, while a problem for all researchers is that research salaries are becoming even less competitive in the market place.

Hospitals, their communities, and health delivery

There is sometimes talk about hospital paediatrics and community paediatrics as though they were two separate entities. Children's hospitals and children's units in general hospitals are community resources, just as schools and shopping centres are community resources. It would be advantageous for the distinction between hospital and community paediatrics to merge, with hospital and community services sharing some staff and resources, while recognising that certain conditions can obviously only be managed in hospitals while for other problems, children are best served by having their health delivery in the community. Some of the challenges that children's hospitals face within their own walls are those of chronic illness causing an increased demand on resources. This includes children with long term handicaps who may require frequent hospital admissions, although occasionally these admissions are for respite and could be better managed in a more homely, respite atmosphere than in a high technology teaching hospital. Children's hospitals are increasingly looking to the community to have some of the needs of these chronically handicapped children met, such as the small, but increasing number of children being ventilated at home. An example is a quadriplegic child with no spontaneous respiratory function who, having had his immediate care in hospital, is able to be cared for at home, with home visiting from a hospital or community based service with appropriate expertise.

Many children with long term chronic illness are now surviving beyond the paediatric age group, so that subsequent hospital and community care will be in adult hospitals or from adult based community services. These include older teenagers with cystic fibrosis and spina bifida, conditions which may be poorly understood by adult specialists and where access to the comprehensive paramedical services and team approach of a children's hospital may not be part of the philosophy of the adult centre. The transition of our patients to adult care is rather like the problem parents face as their children grow up. As our patients grow older we should be teaching them to be less dependent on paediatric services and be willing to start letting go while ensuring that we communicate with and educate our adult colleagues in the hospital and the community, so that our patients can move on to a level of care sufficient for their needs. Regular meetings between paediatricians and adult physicians and transitional, joint clinics will help.

Children's hospitals in Australia have concentrated in the last 15–20 years on building up specialty units so that most have units representing all of the paediatric subspecialties. This has sometimes been at the expense of generalist services. The question is whether there is still room for general paediatricians in children's hospitals. The experience of adult teaching hospitals suggests there is. Most adult teaching hospitals no longer have general physicians so that patients, who may have multiple problems are admitted under the care of a subspecialist who is often unable to take an overview of the patient's problems and coordinate care. The general paediatrician in the teaching hospital is also necessary for role modelling. Most current paediatric trainees are likely to move into general or community paediatric areas as most of the subspecialty units are adequately filled by relatively young subspecialists.

While teaching hospitals have a major inpatient focus, a significant proportion of their work involves outpatients. One way of integrating hospital and community child health services is to decrease the length of stay even further with more emphasis on outreach services, utilising paediatric nursing and medical home care services combined with the development of protocols for high quality ambulatory care. This would achieve improved integration of hospital and community services with specialty staff, who may have an appointment in the community as well as in the hospital, being responsible for ensuring continuity of care using resources which move between the hospital and the community.

The challenges for community child health are even greater. The major one is to determine the effectiveness of community child health services. While screening surveillance is traditionally part of community child health, adequate information systems which give data about outcomes, rather than about throughputs have to be developed. There is little point in screening if we cannot measure the outcome of the screening process.

While it is difficult to measure the value of community child health services, particularly primary and secondary prevention and health promotion, ways of rigorously evaluating these services have to be found. Traditionally, community child health services have not attracted people with experience in investigation and evaluation. However, the newer generation of paediatricians includes some with expertise in epidemiology, research, and biostatistics. As they move into community child health, this will be one of their tasks. The initiative has been taken by the Australian College of Paediatrics by establishing a Faculty of Community Child Health to better integrate hospital and community services. This is particularly important in view of the opinion in some sections of government that doctors are not particulary necessary in child health and that ancillary medical staff, who may be cheaper to employ, can do many of their duties. While this view may have some validity, the generic health worker may have a little knowledge in a wide range of areas but often not enough to make real impact. The challenge for medical staff in community child health is to ensure that they develop methods of rigorous evaluation, quality assurance, and peer review to improve the status and quality of community based child health.

The challenge for hospital and community based child health services is improved integration. While the high and rigorous standards of paediatric teaching centres should move into the community, there is room for some community child health 'in-reach' into the teaching centres as the practical, feet on the ground approach of community based doctors to the problems of children and their families living in the real world has much to teach those working in hospitals.

Child health education

In Australia the primary care of children is provided by general practitioners. Most medical schools in Australia provide between nine and 11 weeks of paediatric teaching and experience. Unless graduates obtain further paediatric training they are likely to be poorly equipped to cope with the range of children's health problems. On the other hand, the steadily increasing number of paediatricians means that there is the potential for some paediatricians to set up in primary care practice rather than as consultants.

As teaching hospitals are the repository for much of the paediatric expertise, the question has to be asked as to why teaching hospitals still see children sent in with problems such as undiagnosed meningitis and poorly treated asthma. To be critical of the standard of child health care in general practice when it is the responsiblity of those with the expertise to ensure that standards of continuing education are high and widely avaliable in a realistic and attractive way, smacks of hypocrisy. However, the provision of continuing education is difficult in times of financial stringency when hospitals are struggling just to provide an adequate level of patient care. It also raises the problem of training versus service. What is the obligation of children's hospitals to provide teaching and training to those working in the community and to their house staff when house staff have to cope with a busy load and when health administrators may feel that house staff are employed primarily to look after patients? Even though there are many programmes of formal and informal teaching, there is a discrepancy between the conditions emphasised (by the nature of the case load) in teaching hospital training and the sort of child health problems seen by a general practitioner or paediatrician working in the community or a country centre. While the general practitioner needs to be familiar with common paediatric conditions and to know which childhood problems need expert help, and while the paediatrician will need to be familiar with the full range of paediatric conditions, may need to be able to initiate ventilation of neonates and cope with paediatric emergencies, there will be considerable emphasis in the community on behavioural and developmental problems in childhood, something which the acute teaching hospital situation gives little opportunity for mastering.

Although the general practitioner is the person best placed to provide primary paediatric care and while those with expertise in paediatrics have a responsibility to ensure that the general practioner's level of training is adequate, the large number of paediatricians currently being trained means that consultant positions will not always be available, so that some may be tempted to move into primary paediatric care. The Workforce Committee of the Australian College of Paediatrics has shown that while there are approximately 600 paediatricians in Australia there are approximately 190 paediatric registrars in training, representing a potential increase of 30% in the total number of paediatricians. Workforce projections, taking into account the age of consultant paediatricians in Australia, show that we are currently training almost double the number of paediatricians required. One partial solution is to reduce the number of paediatric training positions and to increase the expertise of general practitioners, by increasing the number of house staff positions for those aiming for a career in general practice. However, the problem is compounded by neonatal intensive care service requirements where paediatric registrars are appointed to meet these service needs (a paediatrician in training could spend two of the six years training in neonatal intensive care) so that in recent years, the number of registrar positions has increased, with many registrars then going on to complete paediatric training. The challenge is to look at ways of having some aspects of neonatal intensive care performed by others, perhaps suitably trained nurses.

A national child health policy

Australia does not have a national child health policy. The challenge to develop one is a current task of the Child Health Committee of the National Health and Medical Research Council and the Australian Association of Paediatric Teaching Centres. As well as having value in clarifying thinking and coordinating efforts, the development of a national child health policy for children has considerable political value as, once the major child health groups in the country agree on such a policy, political candidates and parties can be publicly asked how much they will support it.

Preliminary work on a national child health policy has outlined these goals.

(1) To develop access to adequate health services for all Australian children, regardless of their financial status or ethnic background, and in doing so, to identify disparity in health status between different community groups and work towards its correction. This is particulary relevant to the health of Aboriginal children where the perinatal and infant mortality rates are much higher than for non-Aboriginal children.

(2) To reduce the frequency of preventable premature mortality (from accidents and suicide), to establish national child safety standards, and support a national poisons information centre.

(3) To reduce the impact of disability. This includes a reduction in the occurrence of new disability by preventative measures as well as a reduction of the impact of established disability by early recognition along with appropriate interventions that are maintained and evaluated. Such conditions include congenital abnormalities, prematurity, chronic illness, intellectual and physical disability as well as learning disorders.

(4) To reduce the impact of vaccine preventable disease.

(5) To reduce the impact of diseases that occur in adulthood but which have their origins or early manifestations in childhood and adolescence. These include conditions associated with nutritional problems, diseases associated with alcohol and tobacco use, conditions associated with unprotected sexual activity, and those associated with poor cardiovascular fitness.

(6) To enhance family and social functioning including adequate parenting, the health needs of foster children and children of divorce, the many different types of families and cultures in Australian society, as well as health problems associated with poor housing, low income, unemployment, and social and educational disadvantage.

These goals are a reminder that optimum child health is much broader than disease treatment and prevention. It means that as well as ensuring access to adequate standards of acute health care for all children, they should be adequately immunised, educated about the hazards of smoking, protected from abuse and neglect, have their learning difficulties addressed, and be protected from injury. Many of these priorities are clearly related to education and welfare, although they are an intregral part of promoting child health.

A national child health strategy must also look at Australia's relationship to Asia. For many years Asia was a place where Australian paediatricians travelling to Europe stopped while their plane was being refuelled. We are now developing a greater understanding of health care in the Asian region and realising that, as residents of this region, we should become more involved in training and education and in sharing knowledge and expertise.

It is difficult to make predictions about challenges for child health in Australia far into the future. When looking back over the last 30 years it becomes apparent that it would have been impossible to predict the amazing advances such as in diagnostic imaging and in molecular biology which have occurred throughout the world and in which Australia has shared. The only thing we can be sure about for the next 30 years is that once again it will probably be impossible to predict the extent of the changes which will occur in paediatrics. However the need for accountability, rigorous evaluation, equity and access of health care to all children will remain whatever the technological advances.

Many of the ideas in this paper are the results of helpful discussions held with Drs W Butt, D Jolly, B Neal, F Oberklaid, and J Yu and Professors A Carmichael, L Landau, J Pearn, P Phelan, D Roberton, and G Vimpani

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LETTERS TO THE EDITOR

Chronic fatigue syndrome: a joint paediatric–psychiatric approach

SIR,—While agreeing that physical, psychological, and social factors must all be taken into account in the management of this complex and controversial syndrome I would disagree with Dr Margaret Vereker's statement that no organic pathology can be detected to account for any of the symptoms. This conclusion has been made without reference to a number of research papers describing persisting viral infection, neuromuscular abnormalities in both structure and function, and immune system dysfunction.

Gow *et al* using polymerase chain reaction techniques, have been able to demonstrate the presence of enteroviral genome in muscle biopsies from a significant number of patients (53%) compared with controls (15%).[2] None of the healthy control group in this study had evidence of viral particles in their muscle—this was only found in those with colonic or breast malignancies Precisely what cytopathological effect this intracellular virus is having within muscle remains open to debate. However, Behan *et al* have published electron microscopic evidence of structural damage to the muscle mitochondria along with type II fibre atrophy[3]; this is a finding which is not normally considered to be consistent with simple disuse.

Equally, it is now accepted that a large number of common viral infections (for example herpes, measles, mumps, and enteroviruses) are all capable of entering, persisting, and multiplying within the central nervous system, often without producing any detectable cytopathological damage. Their effect is on cell function rather than structure, and they particularly affect neurotransmitter activity in areas such as the limbic system and hypothalamus

Details of objective central nervous system pathology have recently begun to emerge from research groups in both the United Kingdom and the United States. Buchwald *et al* have produced evidence of immune dysfunction (a significantly increased CD4/CD8 lymphocyte ratio), reactivation of human herpes virus type 6, and structural CNS abnormalities in a group of well over 200 patients.[4] The magnetic resonance imaging (MRI) brain scans revealed punctate, subcortical areas of high signal intensity consistent with oedema or demyelination in 78%. The authors of this multicentre study concluded that the patients were experiencing a chronic, immunologically mediated inflammatory process in the central nervous system after a viral infection. Furthermore, in a personal communication, Professor Anthony Komaroff, from Harvard, has stated that he believes that these MRI studies indicate central nervous system inflammation.

Evidence of hypothalamic dysfunction has come from both Demitrack *et al* (lowered concentrations of blood cortisol consistent with inadequate hypothalamic-pituitary axis stimulation),[5] and Bakheit *et al* (an upregulation of hypothalamic 5HT receptors using a buspirone challenge).[6] As far as symptomatology is concerned these latter findings may well be significant in view of the often marked disturbances in sleep pattern, appetite, and thermoregulation described in both adults and children with postviral fatigue syndrome.

On behalf of the ME Association could I also correct the author's statement that we regard physical exercise as being 'harmful' and something that 'must be avoided'. My own guidelines on the management of children state quite clearly that . . 'A period of bed rest may well be beneficial in the early stages, but following this, rest and exercise need to be carefully balanced. On the one hand there is a very real danger that prolonged immobility will result in further weakness, wasting and even contractures. On the other there is no doubt that when children do start to recover, there is a great temptation to start suddenly doing too much and precipitate relapse. If children learn to pace themselves, both physically and mentally, they should be able to build on progress, which in turn will have a very beneficial effect on self-confidence.'[7]

Unfortunately, the ME Association continues to attract a great deal of misinformed criticism. Despite this we have established a research fund of nearly £250 000, persuaded the Department of Health to recognise postviral fatigue syndrome (ME/CFS) as 'a debilitating and distressing condition',[8] and vigorously exposed the quack remedies that many patients turn to when orthodox medicine rejects or trivialises their suffering. Although the author is clearly concerned about parents being 'exposed' to our views I would once again emphasise that we recognise that social and psychological factors may well play an important part in this syndrome, especially in children.

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Atrial natriuretic peptide

SIR,—Experimental data suggest that atrial natriuretic peptide (ANP) has pulmonary vasodilator activity.[1-3] We postulated that ANP might have therapeutic potential in severe persistent pulmonary hypertension of the newborn (PPHN).

A boy born at 41 weeks' gestation developed severe PPHN in association with meconium aspiration and perinatal asphyxia. By 5 days of age the hypoxaemia was unresponsive to high dose intravenous prostacyclin (maximum infusion rate 40 ng/kg/min) and aggressive conventional ventilation using an SLE 2000. The alveolar–arterial oxygen difference was 80 kPa (600 mm Hg), which is predictive of a poor outcome.[4] With parental consent, ANP (Shire Pharmaceuticals) was infused in incremental doses, each over 30 minutes, of 10, 20, 40, 80, and 160 ng/kg/min and on the next day of 80, 160, and 320 ng/kg/min. Serial measurements were made of plasma ANP, urine cyclic guanosine monophosphate (cGMP), mean blood pressure, central venous pressure, heart rate, and arterial blood gases.

Mean preinfusion serum ANP concentrations on the two days were 215 and 128 pg/ml; peak plasma ANP was 5929 and 7632 pg/ml. Preinfusion cGMP excretion rates of 0·4–1 nmol/kg/hour increased to 4 nmol/kg/hour and remained raised for two hours. The table shows the clinical measurements preinfusion, at the end of the infusion, and at 40/45, 90, and 230/180 minutes after the end of the infusion.

Blood pressure showed a clinically relevant fall after the end of the infusion on both days. Central venous pressure remained essentially unchanged. Preductal arterial oxygen tension (Pao_2) fell slightly by the end of the infusion on day 1 but 90 minutes later had risen to 17·26 kPa, then falling to 8·23 kPa by 230 minutes. On the second day of infusion Pao_2 rose by 1·73 kPa during the infusion and 180 minutes later remained 1·08 kPa above the preinfusion value. The baby survived to go home.

There has been some experience of ANP infusion in adults but no previous report of ANP infusion in a neonate. Adnot *et al* reported a reduction in pulmonary artery pressure after ANP infusion up to 100 ng/kg/min in adults with pulmonary hypertension secondary to chronic obstructive lung disease.[3] In this group plasma ANP rose to around 3600

Clinical measurements during ANP infusions

	Preinfusion	*End of infusion*	*Minutes after end of infusion*		
Day 1.			*40*	*90*	*230*
Central venous pressure (mm Hg)	8	8	8	8	9
Blood pressure (mm Hg)	56	48	40	48	59
Heart rate/min	178	199	190	204	182
Pao_2 (kPa)	6·79	6·23	7·0	17·26	8·23
Day 2:			*45*	*90*	*180*
Central venous pressure (mm Hg)	6	6	6	5	7
Blood pressure (mm Hg)	54	53	52	45	65
Heart rate/min	175	177	187	170	170
Pao_2 (kPa)	5·7	7·43	6·54	6·46	6·78

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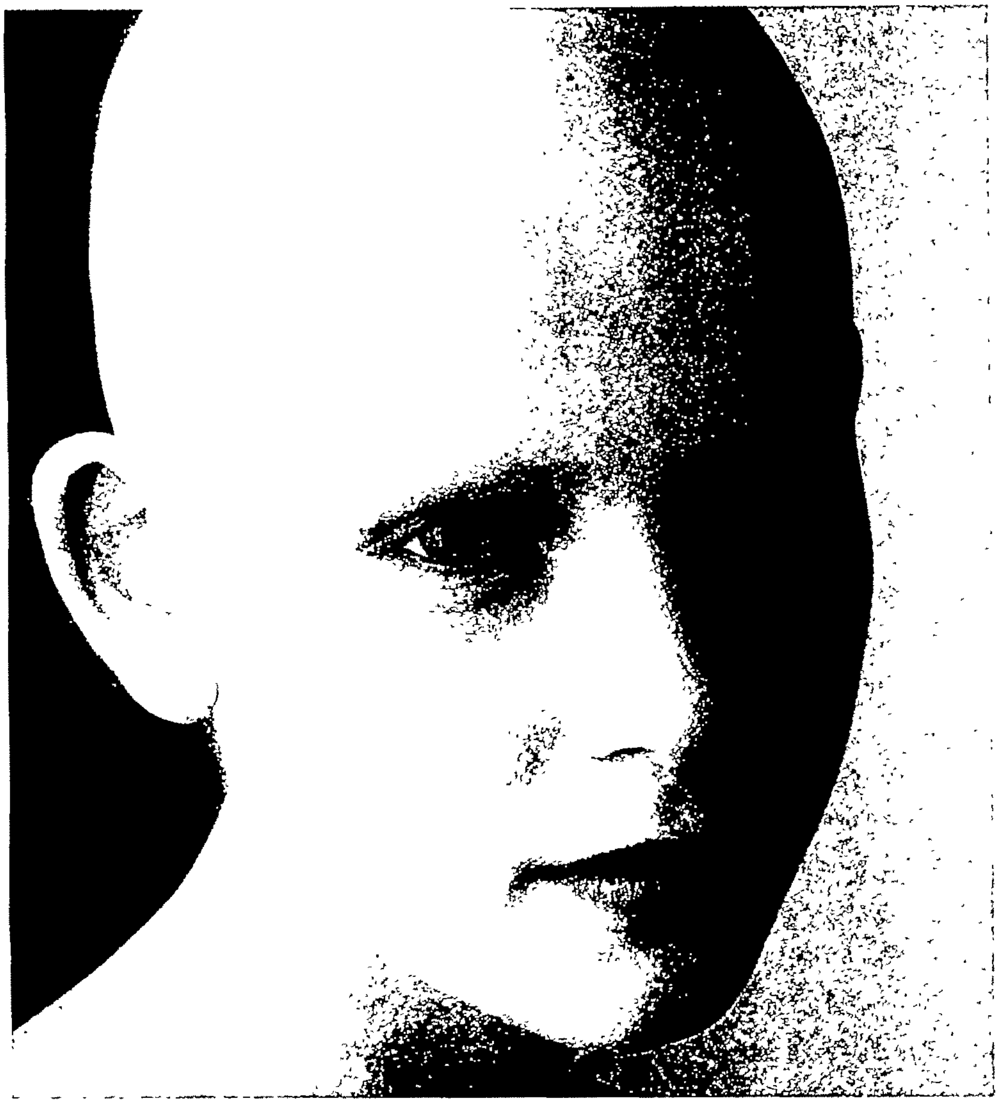

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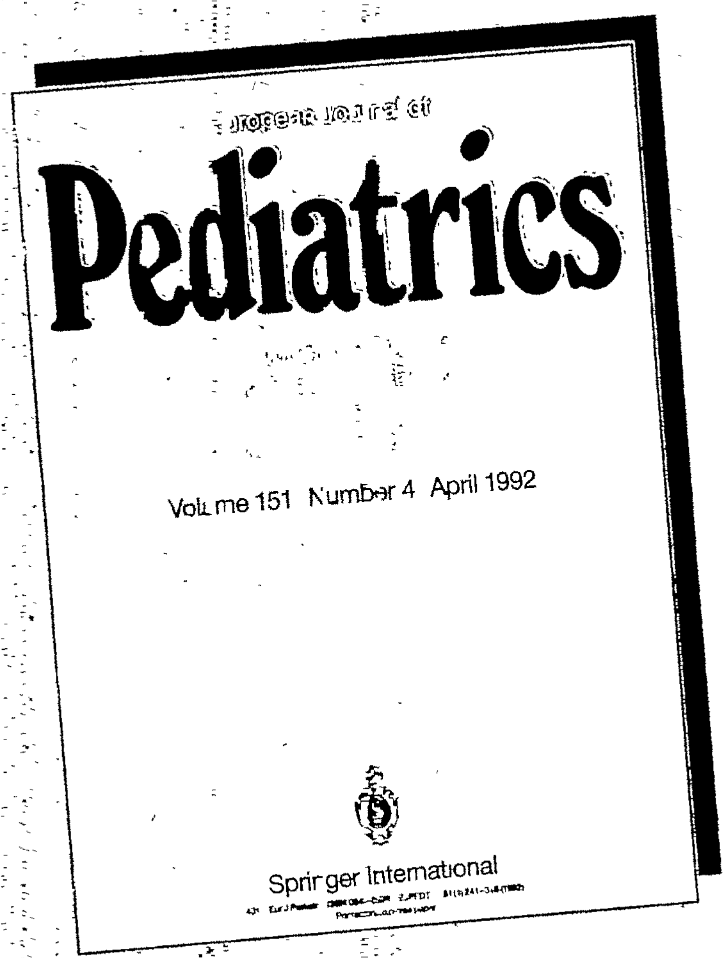

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pg/ml (compared with 2556 and 2888 pg/ml after infusion at 80 ng/kg/min in the neonate reported here). The same workers found ANP infusion to attenuate the pulmonary response to hypoxia in pigs [1]

On the first day of infusion the infant showed a slight fall in PaO_2 at the end of the infusion followed, 90 minutes later, by an appreciable rise that lasted for approximately two hours. The initial fall might be explained by increased perfusion of poorly ventilated lung units[3] but the late rise is difficult to explain, though the cGMP excretion rate did remain raised for two hours A dose dependent relaxation of pulmonary arteries, induced by ANP, has been shown in bovine arterial rings[2] but in our case ANP concentration returned to baseline by around 23 minutes

In this infant high dose ANP infusion was relatively well tolerated. Although we do not claim that this child's satisfactory outcome was related to treatment with ANP, we do believe that ANP should be added to the list of therapeutic options in the management of persistent pulmonary hypertension of the newborn that require further study

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An indirect calorimetry system for ventilator dependent very low birthweight infants

SIR,—While the need for measurement of energy expenditure and nutrient utilisation in sick ventilator dependent infants is undisputed, we have several reservations about the indirect calorimetry system described by Forsyth and Crighton.[1] On p316 is $\dot{V}_E$ the inspired or expired minute ventilation? The equations given appear to take these to be equal, even though this amounts to assuming that the respiratory quotient (RQ) is 1. If instead the inspired and expired volumes of *inert gas* are assumed equal the oxygen consumption (VO_2) can be found as

$$\dot{V}\mathrm{O}_2=V_{\mathrm{inspired}}\left\{\frac{\mathrm{FIO}_2-\mathrm{FEO}_2-\mathrm{FIO}_2.\mathrm{FECO}_2}{1-\mathrm{FEO}_2-\mathrm{FECO}_2}\right\},$$

a similar expression exists for carbon dioxide production. When $\mathrm{FIO}_2=0{\cdot}4$ the equations in the paper underestimate VO_2 by 12% if RQ= 0·7 and overestimate it by 8% if RQ=1·2; calculated values of RQ will be biased towards 1,[2] with true RQs of 0·7 and 1·2 being computed as 0·80 and 1·11 respectively.

In the gas infusion studies reported in table 1 it is unclear how to assess the values calculated for $\dot{V}\mathrm{O}_2$ when nitrogen is infused into the system This part of the study calculates $\dot{V}\mathrm{O}_2$ as if the results were from a patient; the first equation on p318 then allows the calculated $\dot{V}\mathrm{O}_2$ to be checked in terms of nitrogen flow rate and FIO_2. If $\dot{V}\mathrm{O}_2$ is calculated correctly then this check equation is

$$\dot{V}\mathrm{O}_2=\frac{\dot{W}\mathrm{N}_2\ .\ \mathrm{FIO}_2}{1-\mathrm{FIO}_2};$$

if the equations on p316 are used then this becomes:

$$\dot{V}\mathrm{O}_2=\frac{\dot{V}_{\mathrm{inspired}}\dot{W}\mathrm{N}_2\ .\ \mathrm{FIO}_2}{\dot{V}_{\mathrm{inspired}}+\dot{W}\mathrm{N}_2}\cong\dot{W}\mathrm{N}_2\quad\mathrm{FIO}_2.$$

For the nitrogen flow rates given in table 1 (10·10, 14·10 ml/min) and FIO_2 is 0·40, the expected values of $\dot{V}\mathrm{O}_2$ would be, from the first equation, 6·73, 9·40 ml/min and from the approximate version of the second equation, 4·04, 5·64 ml/min. From the results for the higher nitrogen flow rate it would appear that the second equation has been used (as would be consistent with the earlier part of the paper) but the agreement is poor at the lower flow rate.

Finally, we were disappointed that gas infusion studies were performed using only one ventilator setting. Increasing the inspired oxygen concentration (while keeping $\dot{V}\mathrm{O}_2$ constant) causes a reduction in the inspired–expired oxygen difference ($\mathrm{FIO}_2-\mathrm{FEO}_2$) Thus as $\mathrm{FIO}_2-\mathrm{FEO}_2$ decreases, the error sensitivity in the measurement of $\dot{V}\mathrm{O}_2$ is magnified.[3] It is not uncommon for sick ventilated infants to need FIO_2 up to 1·00. The errors in the measurement of energy expenditure at high oxygen concentrations will be markedly increased and this must be acknowledged

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Dr Forsyth comments:

Although the general principles of indirect calorimetry may apply to all systems and subjects, there are some features which require specific consideration depending upon the nature of the system and the size of the subject being studied. In our system for ventilated low birthweight infants,[1] there are at least two important aspects which differ from adult systems, first the effect of changes in RQ on expiratory flow volume ($\dot{V}$E) and second, the validity of excluding FICO_2 from the calorimetry calculations.

Adult calorimetry systems commonly use an inspiratory flow volume ($\dot{V}$I) in the region of 40 l/min, and for a 70 kg individual with an oxygen consumption ($\dot{V}\mathrm{O}_2$) of 320 ml/min and RQ of 0·7, the difference between $\dot{V}$I and $\dot{V}$E will be 96 ml (0·24% of $\dot{V}$I) In our system $\dot{V}$I is 6 l/min (inspiratory flow from the ventilator), and for a 1500 g ventilated infant with a $\dot{V}\mathrm{O}_2$ of 9 ml/min and RQ of 0·7, the difference between $\dot{V}$I and $\dot{V}$E is 2·7 ml, that is 0 045% of $\dot{V}$I In order to correct for this difference, Drs Matthews and Matthews offer a formula based on adult data,[2] and which involves the values of four different measurements Not only is there a risk that the overall error of these measurements may exceed the error induced by the difference in the $\dot{V}$I and $\dot{V}$E flow volumes but their equation is not valid for our system If it is applied to the 1500 g infant, the 'corrected' $\dot{V}\mathrm{O}_2$ will be 7·79 ml/min compared with the actual $\dot{V}\mathrm{O}_2$ of 9 0 ml/min (an underestimate of 13 3%). This underestimate is constant, and not limited to the margins of RQ. Using our simpler equation the calculated $\dot{V}\mathrm{O}_2$ at RQ 0·7 is 7·9 ml/min (underestimate 12%), but this error reduces to 0% as the RQ approaches 1·0. The large persistent error with the Matthews' equation is due to the omission of FICO_2. In adults this is usually less than 1% of FECO_2 and commonly ignored, but for a low birthweight infant in our system the FICO_2 can account for up to 22% of FECO_2. The formula should therefore be corrected to

$$\dot{V}\mathrm{O}_2=V_I\left\{\frac{\mathrm{FIO}_2-\mathrm{FEO}_2-\mathrm{FIO}_2.\mathrm{FECO}_2+\mathrm{FEO}_2.\mathrm{FICO}_2}{1-\mathrm{FEO}_2-\mathrm{FECO}_2}\right\}$$

A simpler and potentially more accurate adjustment is the traditional Haldane correction, $\dot{V}\mathrm{I}=\dot{V}\mathrm{E}.\mathrm{FEN}_2/\mathrm{FIN}_2$, and as our system is continually measuring inspiratory and expiratory nitrogen this can be easily accommodated.

During the nitrogen infusion study the mean FIO_2 was 0·421 and $\dot{V}$E 5·257 l/min. By using the measured values for $\dot{V}$E, FIO_2, and FEO_2 the predicted $\dot{W}\mathrm{N}_2$ were compared with the actual $\dot{W}\mathrm{N}_2$, and using our last equation the actual oxygen consumption as opposed to the simulated $\dot{V}\mathrm{O}_2$ was confirmed to be zero The $\dot{V}\mathrm{O}_2$ data reported with the nitrogen infusions were calculated as for an infant study using the described software calculations and were included, albeit with the limitations as discussed above, to relate the infusion data to actual levels of $\dot{V}\mathrm{O}_2$ which are seen in low birthweight infants. Unfortunately we did transcribe the wrong data point for the $\dot{V}\mathrm{O}_2$ for the nitrogen infusion of 10·1 ml/min and this should have been 4 20 (0·22) ml/min. We are grateful for this being drawn to our attention.

Although we will shortly be providing clinical and technical data on the use of our system with higher levels of FIO_2, it is our experience that in the present surfactant era considerably fewer babies are requiring a very high FIO_2 for a long period of time. We realise that some babies do require an FIO_2 as high as 1·0, but we believe that for those babies there are more urgent priorities than a measurement of energy expenditure.

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2 Ferrannini E The theorectical basis of indirect calorimetry: a review *Metabolism* 1988;37: 287–301

Imposed upper airway obstruction and covert video surveillance

SIR,—Covert video surveillance (CVS) may be extremely useful and is often the only method to prove that some cases of apparent life threatening events (ALTE) are caused by imposed upper airway obstruction. Samuels *et al*, recently reported 14 cases which they documented in this manner.[1]

Within a period of six months we have seen three babies with ALTE from three unrelated families. All three had been discovered limp, cyanotic, and apparently lifeless during their afternoon nap. Petechial haemorrhages were found on the face and neck of two of the babies on admission. No other episodes occurred during observation in hospital or the follow up period.

These would probably have remained unexplained unrelated cases were it not that when the third case was brought to the casualty department by the family doctor he was accompanied by the babysitter who had discovered the baby. She was recognised by one of the nursing staff as a regular attender at the casualty department with minor wounds that were suspected of being caused by automutilation and she had made several allegations of being attacked or raped.

In the ensuing discussions it came to light that this woman was the babysitter who had also been involved in the first two cases. She has since been investigated by the police. However, in spite of strong suspicions of imposed upper airway obstruction of the babies by her, there has been insufficient evidence to bring her to trial.

CVS as described by Southall *et al*[2] would have failed in these cases, because it is usually only the parents or very close relatives who are allowed to be continually present with the baby in hospital. Very thorough history taking especially concerning the surrounding circumstances remains extremely important in investigating every case of ALTE especially if imposed upper airway obstruction is suspected.

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1 Samuels MP, Mc Claughlin W, Jacobson RR, Poets CF, Southall DP Fourteen cases of imposed upper airways obstruction. *Arch Dis Child* 1992;67:162–70
2 Southall DP, Stebbens VA, Rees SV, Lang MH, Warner JO, Shinebourne EA. Apnoeic episodes induced by smothering: two cases identified by covert video surveillance *BMJ* 1987;294: 1637–41

Anal abnormalities in childhood myotonic dystrophy

SIR,—The paper by Reardon and colleagues on abnormal anal signs seen in myotonic dystrophy is worrying on several counts.[1] The physical signs are described inadequately which makes interpretation of the paper difficult. The Royal College of Physicians report,[2] while referenced, is not heeded in the need for a consensus on definition and method of examination. Thus 'a reflex dilation of the anus was observed on parting the buttocks'. How was the child examined, for how long, and was this a dynamic sign and what degree of dilation was observed? It is noteworthy that only one child in six was said to demonstrate this sign but all had anal laxity.

The illustration shows a degree of anal laxity we have never seen, is this laxity or dilation? Was this degree of gaping achieved on merely parting the buttocks? Was the child constipated and demonstrating the 'visibly relaxed anus' of Clayden?[3] This child was 15 years old and had had a lifetime of soiling, what had earlier examinations revealed and to what treatments and manoeuvres had she been subjected?

Single physical signs are rarely diagnostic and in making a diagnosis of child sexual abuse the jigsaw must be carefully constructed.[4] To begin an investigation on the basis of a child with a known bowel dysfunction and anal laxity is clearly problematic but in the context of a girl who is alleging abuse it is, in child protection terms, quite proper. Advice to doctors stated 'It is important to take what the child says very seriously, and to spend time listening to what the child has to say '[5] It is also evident that children with special needs are at risk of abuse and to recognise abuse in children with communication problems requires particular skill.[6] Children do need protection from the trauma of wrongful diagnosis but similarly physicians have until recently failed their patients by their inability to recognise maltreatment

Finally, what proportion of children with myotonic dystrophy have bowel disorders or an abnormal anus on examination? What proportion have no abnormality? The association of two conditions does occur.

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1 Reardon W, Hughes HE, Green SH, Lloyd Woolley V, Harper PS Anal abnormalities in childhood myotonic dystrophy—a possible source of confusion in child sexual abuse *Arch Dis Child* 1992,67:527–8.
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Drs Reardon, Hughes, and Green and Professor Harper comment:

The comments of Drs Wynne and Hobbs reflect the difficulties with which clinicians are obliged to grapple in attempting to confirm or refute a suspected diagnosis of child sexual abuse. Foremost among these is the non-specificity of single clinical signs. However, in many instances, abnormalities of anal physiology do contribute significantly to decisions with far reaching effects for patients and families. It is precisely because we absolutely agree with Drs Wynne and Hobbs that 'children need protection from the trauma of wrongful diagnosis' and because of the central role which anal abnormalities and interpretation thereof often has in reaching diagnoses of sexual abuse that we felt prompted to submit our report.

The report did not pretend to be a scientific treatise of anal sphincter dysfunction in myotonic dystrophy Our hope in sharing these non-specific clinical observations is to make colleagues aware of added potential pitfalls which attend the diagnosis of child sexual abuse in myotonic dystrophy. We feel that shared clinical experiences such as ours are of value to clinicians in avoiding inappropriate diagnoses of child sexual abuse.

Archives of Disease in Childhood 1992; 67: 1412

Prostacyclin concentrations in haemolytic uraemic syndrome after acute shigellosis

SIR,—Although the epidemiology of certain forms of the haemolytic uraemic syndrome (HUS) has become clearer in recent times, pathogenic details remain largely unresolved. The role, if any, of prostacyclin (PGI2) in the diarrhoea-associated forms of HUS (D+HUS) cannot be deduced from previous reports and the study by Alam *et al* on patients with shigella induced HUS adds to the confusion.[1] In the following we acknowledge, however, that in past European and American studies the aetiology of D+HUS is likely to be verocytotoxin producing *Escherichia coli*, which although similar is not homologous with shigella induced HUS.

Prostacyclin is probably not a circulating hormone in man: its plasma half life is brief and intact molecules cannot be measured directly in clinical practice. Thus the term 'prostacyclin concentration' is at best an extrapolation. Two main approaches have been used to identify abnormalities of PGI2 metabolism in disease states. The more direct of these is to measure stable degradation products such as 6-keto PGF-1α in biological fluids. The commonly used radioimmunoassay kits give plasma estimates which exceed those of the more specific gas chromatography and mass spectrometry. Blood sampling in itself induces artifacts, and although the urinary excretion of degradation products may be more consistent in health, this is unlikely to be a reliable method when renal function is rapidly changing. Both Stuart *et al*[2] and Turi *et al*[3] found plasma concentrations of prostacyclin metabolite to be increased in D+HUS at onset.

The second approach has been to determine whether plasma or serum stimulates generation of prostacyclin by endothelial tissue in vitro. Prostacyclin release into the supernatant medium is measured indirectly either by bioassay or as 6-keto PGF-1α. Published results are conflicting; Schlegel *et al*[4] and Levin[5] found that prostacyclin generation was promoted by plasma, whereas Turi *et al*[2] and Siegler *et al*[6] showed reduced production. Methodological differences may explain these inconsistent findings, but abnormalities of plasma stimulating factors or inhibitors have in any case not been shown to reflect disturbances of prostacyclin metabolism in vivo.

Unfortunately Alam *et al* did not make clear which method they used. The result section and abstract refer to plasma concentrations of 6-keto PGF-1α suggesting direct measurement. However, their method refers to radioimmunoassay for 'prostacyclin', but also to generation of 6-keto PGF-1α by rabbit aortic rings in response to patients' plasma.

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1 Alam AN, Abdal NM, Wahed MA, *et al*. Prostacyclin concentrations in haemolytic uraemic syndrome after acute shigellosis in children. *Arch Dis Child* 1991;66:1231–4
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4 Schlegel N, Maclouf J, Loirat C, *et al.* Absence of plasma prostacyclin stimulating activity deficiency in hemolytic uremic syndrome *J Pediatr* 1987;111:71–7
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Interleukin-1α and soluble interleukin-2 receptor in atopic dermatitis

SIR,—Dr Agata and colleagues reported enhanced interleukin-2 (IL-2) activity in blood mononuclear cells from patients with food sensitive atopic dermatitis following allergen exposure.[1] Soluble interleukin-2 receptor (sIL-2R) is an indirect marker of T cell activation by IL-2 and raised concentrations have previously been described in adults with atopic dermatitis.[2] However, in vitro studies suggest that IL-2 secretion by T helper cells is not only antigen driven but it is also dependent on interleukin-1 (IL-1) expression by cells of the macrophage/monocyte series; IL-1 also upregulates the expression of high affinity receptors for IL-2 on T helper cells type 1.[3] In order to investigate this hypothesis, we measured IL-1α and sIL-2R using an ELISA technique. Twenty three children were assessed: 11 with atopic dermatitis and 12 non-atopic normal controls. The results are shown in the table.

	Controls	*Atopic dermatitis*	*Unpaired t p value*
Mean age (years)	9·2	8·6	NS
Range	4–14	4–16	
IL-1α (pg/ml)	163	369	p<0 02
95% CI	56 to 269	232 to 505	
sIL-2R (U/ml)	189	377	p<0·02
95% CI	75 to 301	262 to 492	

CI=confidence interval.

There was a strong direct correlation between IL-1α and sIL-2R (*r*=0·67, p<0·001) which suggests that expression of the two are dependent. While no apparent relationship existed between either cytokine concentration and disease severity using the criteria of Rajka and Langeland[4] or IgE concentrations, our results demonstrate that there is enhanced endogenous secretion of IL-1α, and increased stimulation of IL-2 receptors, in children with atopic dermatitis These findings suggest that these cytokines may contribute to the inflammatory process in atopic dermatitis and are consistent with the observations of Dr Agata and colleagues.

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Pulse oximetry reference values at high altitude

SIR,—Lozano *et al* in their article on pulse oximetry reference values at high altitude conclude that their reference values could be used for the interpretation of oxygen saturation at high altitude in Bogota and other cities at a similar altitude.[1] However, the authors have failed to take into account potential sources of error.

The fall in arterial oxygen saturation at altitude is due to the fall in barometric pressure rather than the gain in altitude *per se*. There is a corresponding fall in atmospheric oxygen tension (Po_2) with fall in barometric pressure (at 2000 m atmospheric Po_2=124·9 mm Hg (16·6 kPa) and at 3000 m Po_2=110·2 mm Hg (14·7 kPa)[2]) such that the author's proposed reference ranges are not suitable for use at altitudes other than that of Bogota (2640 m) as even small changes in altitude will alter the availability of atmospheric oxygen and the arterial oxygen saturation

Furthermore, at a given altitude the barometric pressure changes with local variations in weather and to a greater extent with the season such that in mid-summer the barometric pressure may be 11 mm Hg (1·47 kPa) higher than in winter.[3] Moreover, there is an equatorial bulge in the atmosphere such that the barometric pressure at a given altitude near the equator is higher than at the same altitude nearer the poles by 17 mm Hg (2·27 kPa) [4] These pressure variations will affect the partial pressure of oxygen in the atmosphere. Although of little significance at sea level pressures, these changes in atmospheric Po_2 in the already 'desaturated' infant at altitude may significantly affect arterial saturation

Taking these observations into account the authors may find that there are both seasonal and latitudinal variations in arterial oxygen saturation along with the changes in barometric pressure such that their proposed reference ranges should be intrepreted with caution in summer and probably not used at all at latitudes or altitudes distant from Bogota.

Before recognition of these changes in barometric pressure with season and latitude the ascent of Everest (8848 m) without supplementary oxygen was thought impossible. In 1978 Messner and Habeler proved the physiologists wrong.[5]

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1 Lozano JM, Duque OR, Buitrago T, Behaine S. Pulse oximetry reference values at high altitude *Arch Dis Child* 1992,67:299–301.
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5 Messner R *Everest. expedition to the ultimate* London. Kaye and Ward, 1979.

Randomised trial of nutrition for preterm infants after discharge

SIR,—This interesting study draws attention to a possible need for preterm infants to be fed a slightly higher protein, mineral, and energy-containing milk in the first nine months after birth.[1] However, the authors include detailed tables on feed tolerance, stool number, size and consistency, and skinfold thickness (which show no significant differences between diet groups) yet choose not to present any data on growth of weight, length, and head circumference on which they base their conclusions of a possible advantage for this specially designed formula. It is not enough to say that differences are apparent on visual inspection of the charts. In fact, looking at these it seems to me that if there are any differences at all they take place for length and head circumference only in the first few weeks: after this the curves virtually parallel each other. Weight does fall off in those fed the standard infant formula but only between about 6 and 18 weeks. Growth data have been meticulously collected and the statistical methods explained in detail but without giving information, on velocity or incremental growth, it is difficult to evaluate the findings of the study.

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1 Lucas A, Bishop NJ, King FJ, Cole T. Randomised trial of nutrition for preterm infants after discharge *Arch Dis Child* 1992;67: 324–7.

Drs Lucas, Bishop, and Cole comment:

Professor Davies seeks further information on growth in our study on postdischarge nutrition. The growth data collected at two weekly intervals are shown in our paper graphically (tabulation would have been cumbersome and the graphic data show centile placing). Given the small sample size, as expected, relatively few individual two week measurements showed a significant difference between groups. Nevertheless, in view of the consistently increased weight, length, and head circumference at every two week period up to 9 months' corrected age in the infants fed the fortified diet, we explored whether the overall growth trajectory was different between groups. This is a statistically robust procedure as, unlike the *t* test comparisons of individual two weekly data points, we were taking the entire growth data set for each diet group into account. As growth trajectory is not linear, but curvilinear, growth velocity was calculated from a quadratic fit of the data. The significant differences we reported in length and weight gains between feed groups would be difficult to describe numerically, short of presenting equations for the quadratic curves, and we elected not to. We emphasise, however, that our statistical analyses confirm a clear advantage in weight and length gain (p<0·005 and p<0·01 respectively) for infants fed the fortified formula. The difference between groups in rate of head growth did not achieve significance, because the early divergence between groups tended to diminish later in the study period. Nevertheless, the head growth issue needs further exploration especially in view of our unpublished analyses that show a trend towards higher gross motor development scores at 9 months in infants fed the fortified diet; but many more subjects would be required to test these aspects adequately.

We should be very happy to discuss our growth data in greater depth with individual investigators.

Growth patterns after surgery for virilising adrenocortical adenoma

Sir,—We agree with the notion of Salt *et al* in their article on growth patterns after surgery for virilising adrenocortical adenomas that more information is needed on the natural history of growth and pubertal development in these children.[1] We therefore have recently published observations on growth in 10 children aged 0·8 to 11·8 years with hormonally active adrenocortical tumours (nine carcinomas, one adenoma) before and after surgery (excess of androgens 10/10, of glucocorticoids 5/10, of estrogens 1/10).[2] In addition, five of 10 patients had a palpable abdominal tumour at the time of initial presentation. In only one patient increased longitudinal growth alone had initiated the diagnostic workup.

Only two of our patients had a preoperative height SD score $>+2$. In one patient, an increase in height SD score above baseline was noted simultaneously with the first signs of precocious sexual maturation. However, in five of seven patients followed up postoperatively, in whom removal of the tumour controlled symptoms of hormone excess, height SD score initially declined after surgery. We took this as evidence for catch-down growth, comparable with that in patients with congenital adrenal hyperplasia and delayed initiation of treatment.[3] Although Salt *et al* state that no catch-down growth had occurred in their patients,[1] at least in five of them a period of rapid growth was followed by normalisation of growth velocity and a trend for the bone age to come back in line with the chronological age, similar to our patients. The fact that in most of their patients final height SD score was higher than height SD score at the time of diagnosis is no evidence against postoperative catch-down growth, as at that time the majority of patients were of an age at which most children may not have shifted yet to the definitive centile range that they tend to follow for the remainder of their growth.

Finally, the course of the two patients described by Salt *et al* who had androgen and glucocorticoid excess agrees with our observation that in instances where high concentrations of both hormones affect the growing bone simultaneously, the androgen effect on linear growth and bone maturation appears to dominate. This is different from normal puberty, where hypercortisolism can inhibit longitudinal growth in the presence of physiological concentrations of gonadal steroids.[4]

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1 Salt AT, Savage MO, Grant DB. Growth patterns after surgery for virilising adrenocortical adenoma. *Arch Dis Child* 1992;67:234–6.
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Terbutaline sulphate Turbuhaler in severe acute asthma

Sir,—Pedersen *et al* have shown the efficacy of 0·25 mg of terbutaline administered by Turbuhaler (Astra) in acute asthma.[1] We similarly treated 20 patients with a mean age of 9·9 years (range 5–15) who had acute asthma and severe airway flow limitation.[2] They were taking prophylactic drugs (inhaled nedocromil sodium and/or budesonide) and inhaled β_2 agonists before coming to our unit.

Spirometry (Vitalograph) was performed (best out of three) at 0, 30, and 60 minutes before each dose of terbutaline and again at 90 minutes. The patients inhaled 2·5 mg of terbutaline sulphate (five doses of 0·5 mg/2 minutes), followed by a further 2·5 mg and 1 mg (two doses of 0·5 mg/2 minutes) at 0, 30, and 60 minutes. The results, as a percentage of predicted values, are shown in the table. One way analysis of variance of repeated measures and adjacent difference contrasts for pairs showed significant differences ($p<0·05$) between pairs for all but the 60–90 minute pair for $FEF_{25\%-75\%}$.

Results of spirometry

	Time (min)			
	0	*30*	*60*	*90*
FVC	66·4	89·2	96 8	102·7
FEV_1	50·2	72·4	82 3	87·8
PEFR	50 0	70·3	77·7	86 0
$FEF_{25\%-75\%}$	32·5	56 3	67 6	71 7

FVC=forced vital capacity, FEV_1=force expiratory volume in one second, PEFR=peak expiratory flow rate, $FEF_{25\%-75\%}$=force expiratory flow between 25% and 75% of the forced vital capacity

In two cases, despite clinical improvement, there were no important changes in spirometry even after the administration of 0·5 mg nebulised salbutamol.

Clinically, all patients achieved a normal breathing pattern between the first and third dose without side effects.

In conclusion, the Turbuhaler seems to be effective in severe acute asthma.

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1 Pedersen S, Hansen OR, Fuglsang G. Influence of inspiratory flow rate upon the effect of a turbuhaler. *Arch Dis Child* 1990;65:308–10.
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BOOK REVIEWS

Child Psychiatry and the Law. 2nd Ed. Edited by Dora Black, Stephen Wolkind, and Jean Harris Hendricks. (Pp 200, £10 paperback.) The Royal College of Psychiatrists, 1991. ISBN 0–902241–41–9.

Child Psychiatry and the Law is a distillation of theory and practice that will carry the new or experienced practitioner through the rigours of report writing or presentation in court with confidence. This excellent second edition has followed hard on the heels of the Children Act which came into force in October 1991, and which is affecting the practice of all those who work with children and their families.

There has been a thorough revision of the text encompassing not only changes and debate arising from the Children Act but also from other new legislation, from case law, clinical practice, and research. There is a welcome increase in the discussion of international, transracial, and transcultural issues.

The book is divided into two sections. Section 1 gives general advice on report preparation and on attendance in court, followed by chapters on specific areas, for example, juvenile justice. It is an excellent 'how to . . .' guide, giving advice from the most sophisticated to the most mundane, with useful checklists at the end of most chapters and cross references between chapters. The chapter on children and the law is rather disappointing. The prose is legalistic, losing the sensitivity and clarity which characterises much of the text. Section two consists of examples of specimen reports, which are all the more interesting for the inclusion of information on outcome. The updated reference list complements the careful discussion of the important issues to be considered in the preparation of reports, etc. There is also a useful glossary of terms at the end.

However, the scope of *Child Psychiatry and the Law* goes beyond reports and court work. It explores the role of the child psychiatrist as a professional, independent from the judiciary, and social services. The emphasis is firmly on the child psychiatrist's primary goal being the best interest of the child, and it challenges the practitioner to make the most of opportunities to maximise his or her influence where possible.

With its emphasis on good practice, the book is of value to all child psychiatrists, whether or not they practice in England and Wales. It will be of interest also for professionals working with children and their families in the light of the new Children Act, and, for those requiring the services of a child psychiatrist, it gives an indication of what may be expected of them.

The law is constantly evolving, through legislation, through interpretation by the courts, and through practice At the time of writing this review, there is further controversy over the issue of consent by minors following the Court of Appeal's judgment *Re J* (the anorexic teenager). In the autumn of this year there will be a new Criminal Justice Act which will lead to further changes, especially in the field of abuse work. *Child Psychiatry and the Law* will require regular revision, but this second edition is a timely aid for professionals coping with the complex world of the child in our society now, and sets the standard to which we should all aspire.

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Effective Care of the Newborn Infant. Edited by John C Sinclair and Michael B Bracken. (Pp 650; £95 hardback.) Oxford University Press, 1992. ISBN 0–19–261737–0.

Effective Care in Pregnancy and Childbirth was published in two volumes in 1989 and was immediately recognised as a major work of reference of considerable importance. Indeed, the Department of Health was so impressed by it, they sent a free copy to every obstetric unit in the country which, at £225 for the set, was really quite generous of them.

Effective Care of the Newborn Infant is the neonatal companion to this obstetric book and is an equally outstanding publication. Every neonatal unit should have a copy but don't rush out and buy it just yet for, who knows, the Department of Health may do for paediatrics what they've done for obstetrics and send us all a free copy! At only £95 it is cheap at the price In fact, you do need all three volumes to cover the whole of neonatology.

Effective Care of the Newborn Infant is not a standard textbook of neonatal paediatrics, it is primarily a book on treatment and is based opon the statistical technique of meta-analysis. The authors have reviewed all the randomised trails on neonatal care that they could find in the literature and have carried out some 2000 new analyses of them. From these analyses, overviews are presented and conclusions drawn as to what, on the present evidence, is the best treatment for any particular condition. The book is in three sections: methods, interventions, and diseases. There are 38 contributors, 31 of them come from North America and, while neonatal practice over there is not the same as in Europe, in this case the differences don't seem to matter because they have analysed the vast majority of the world literature to produce their reviews, presenting the evidence for the reader to see for himself All the contributors have also used a standardised approach to review the evidence on their own topic.

The first section, on methods, which is only 15 pages long, describes the principles used in writing the book and explains how the published evidence has been assessed, and the statistical methods used to analyse the effects of the various treatments, and so produce the overviews. If, like me, you are not entirely clear what a meta-analysis is, it is fully explained in this section. The interventions that have been analysed in this way cover· care in the delivery room and resuscitation, thermal environment, fluid therapy, various aspects of feeding, oxygen administration, and mechanical ventilation. There is also an interesting chapter analysing studies that have been done on 'bonding', and 'attachment'. The diseases whose management has been reviewed include: birth asphyxia, patent ductus arteriosus, respiratory distress syndrome and other acute lung disorders, apnoeic attacks, blood disorders, jaundice, infections, necrotising enterocolitis, glucose homoeostasis, periventricular haemorrhage, and retinopathy of prematurity.

Within each chapter there is an introduction to the clinical problem but only sufficient to provide a background to the various managements that have been tried. These are then reviewed in some detail based on the meta-analyses of the literature. Each chapter ends with a short summary with implications for current practice and future research, and as might be expected, the list of references is extensive

Neonatology is a rapidly developing specialty and the number of new publications on the subject each year must be enormous. It is inevitable therefore that a book of this nature will need to be regularly updated if it is to maintain its present status as a major reference work.

As mentioned earlier, this is not a textbook of neonatology, for example there is nothing in it on malformations, but what it does tell you is the present consensus on how to manage a particular condition, and it will be invaluable to anyone drawing up his, or her, department's protocols and management guidelines. It will certainly change many opinions on present practice and I suspect there are some personal practices that will find no support For example, on sodium bicarbonate they say, 'there is no evidence of any benefit, we do not recommend its use' hurrah; it is also great for ending arguments on neonatal ward rounds.

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The CaF Directory of Specific Conditions and Rare Syndromes in Children with their Family Support Networks. Edited by Christine Lavery, Harry Marsh, and Caro Youngs. Published by Contact a Family, 1991 (A5 loose leaf pages indexed in a ring binder. ISBN 0–964–0703. £45 plus £3 postage. Optional £10 per annum for two six monthl updates. (Contact a Family. 16 Strutton Ground, London SW1P 2HP.)

'Like a bomb hitting', is how parents remember the diagnosis of a disabling or fatal condition in their child. For the affected family the diagnosis of any one of a thousand rare syndromes can be the trigger for bewilderment, depression, and even anger. Contact a Family, that has done so much to put families in touch with sources of information and emotional support, has now produced a catalogue of all the support groups available to families. Anybody involved in the diagnosis of such a condition will need this directory close to hand.

Nearly 200 organisations and the umbrella organisations that act for the more frequent neurological, cardiac, and metabolic conditions have been included. For each condition listed there is a page of background information and a contact address or phone number. The specific society will usually be able to provide the family and their support team with more detailed advice about the condition and its management. The support association will often have more experience in the rare conditions than those carers available locally. This partnership can complement the general practitioner and the general paediatrician. Contact with other families allows parents to share their thoughts and fears, and work through their grief, but each family must be allowed to dictate the pace at which they can cope with this information. The directory should not be a substitute for sympathetic counselling on our part. A medical and genetic glossary together with a cross referenced index will allow non-clinical readers to find their appropriate entry. The directory has been produced as a loose leaf folder, ideal for photocopying individual entries (and Contact a Family approves of this). Update sheets are planned every six months. I could not think of any condition for which you would not be able to find help somewhere in this directory.

This directory emphasises the need of the family to have a name for their child's condition. Which organisation should we suggest for the child with multiple problems, where investigations are continuing or where no unifying diagnosis can be made? If used inappropriately the directory might invite parents to 'shop around' among the support groups for their own diagnosis. Perhaps it would be a compromise to let families skim through the index and try to find the best niche for them. We have no control over what the individual groups will be saying to families. Small societies and individuals with rare conditions may give a very directive account based only on their own experiences. I understand that there is an informal vetting process of the organisations listed by Contact a Family. References to the availability to prenatal diagnosis are likely to go quickly out of date. It would be safer to ask families to seek specific advice, before starting another pregnancy. The £45 price does seem expensive, but it represents money well spent by every paediatric department and community assessment unit.

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Protein Energy Malnutrition. By J C Waterlow. (Pp 407; £50 hardback.) Edward Arnold, 1992. ISBN 0-340-50127-8.

This is a spendid book. Although entitled *Protein Energy Malnutrition*, it covers much more than might be suggested by the title and is the distillation of a lifetime spent in research and clinical involvement with nutrition. The book is not only a useful reference manual for those whose pratice includes children with kwashiorkor, marasmus or undernutrition (the problems embraced by the title), but provides a thought provoking read for those with no experience of childhood malnutrition but who are interested in nutritional physiology. Professor Waterlow's experience with malnutrition must be almost without comparison and he is as ready to question his own research hypotheses and experiences as those of others; the book frequently presents the author's personal views in a stimulating, undogmatic way.

Early chapters discussed the physiology and pathology of protein energy malnutrition, changes in body composition, changes in organ function and in metabolism, the role of free radical activity, and the pathogenesis of the oedema of kwashiorkor. After a practical chapter on management, the book continues with a wide ranging discussion of issues relevant to the prevention and prognosis in protein energy malnutrition, infant feeding, nutrition and infection (with A M Tomkins), and the effects of malnutrition on mental development (with S Grantham Macgregor). The chapter on the anthropometric assessment of nutritional status is a uniquely, clear description of the problems and pitfalls of the various methods available for assessment and is presented in a way comprehensible to non-statisticians.

This is the third book on protein energy malnutrition published by Edward Arnold; the second and third books are not later editions or updates of the first, but totally new books. Waterlow describes his book as a personal review which includes some accounts of the heated debates of the last two decades on the strategy and tactics for the prevention of protein energy malnutrition–debates in which he often featured as a major protagonist. The last chapter, on the prevention of malnutrition, highlights the issues behind these debates. It is sometimes stated that for all the research, nutritional science has done nothing to help the malnourished of the world. This is unfair. Nutritional research has provided guidance on the foods which should be used in the prevention and treatment of malnutrition, as well as guidance on the diagnosis of significant malnutrition, and had made advances in the management of malnourished individuals. Its failure is that it has been no more successful than other disciplines in providing peace, economic development, stability, agricultural success, and population control. But nutritionists are the ones who have shown that it is not through medical or nutritional management, but through political, economic, and environmental measures that the massive problems created by malnutrition today will be solved.

Let us hope that, when Edward Arnold publish their fourth book on protein energy malnutrition, the problems and debates on prevention will be history, Sadly I cannot believe this will be so.

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ARCHIVES OF
DISEASE IN
CHILDHOOD

The Journal of the British Paediatric Association

Annotations

The place of computed tomography and lumbar puncture in suspected bacterial meningitis

Although the incidence of acute bacterial meningitis has not changed significantly over the last 40 years, the death rate had declined considerably,[1] presumably due to earlier diagnosis and advances in antibiotic treatment and paediatric intensive care. Between the years 1971 and 1986 the overall mortality from bacterial meningitis in children aged under 13 years in the North East region of Scotland was only 1·8% compared with 11·9% for the period 1946–61.[1] In England and Wales between 1985 and 1987 the case fatality rate for infants with bacterial meningitis 1–12 months of age (a high risk group) was only 5·4%.[2] As well as deaths in hospital, both these studies included cases of rapid death at home found to have meningitis at subsequent coroner's postmortem examination. Similar low mortality rates have been reported from Sweden[3] and the United States.[4] The causes of death include septic shock, massive cerebral oedema, and brain coning. Agents such as corticosteroids[5] and human monoclonal IgM antibody to endotoxin[6] are currently being studied for their ability to prevent or reduce septic shock and will not be discussed further here. Might it be possible to reduce the mortality from cerebral oedema and brain coning?

Risk of coning

Raised intracranial pressure is the rule rather than the exception in children with acute bacterial meningitis. Minns *et al* studied 35 children and infants with pyogenic meningitis using a strain guage pressure transducer connected to the end of the spinal needle.[7] Pressures were measured at the time of the initial diagnostic lumbar puncture in all the children and a number also had sequential measurements. Pressures were raised in 33 children with a median pressure of 15 mm Hg, range 4–70 mm Hg (mean upper normal limit of cerebrospinal fluid pressure was taken as 5·8 mm Hg for infants and 6·4 mm Hg for children). The initial pressures were usually higher than subsequent ones but pressures tended to vary throughout the illness. Cerebral perfusion pressures were calculated and in all but two children were acceptable (that is above 30 mm Hg). These data were thought to reflect a Cushing response (that is a reflex rise in systemic arterial pressure in response to raised intracranial pressure) acting to maintain cerebral blood flow. The response to intravenous mannitol was assessed in 15 patients with raised pressure. In some patients the pressure took as long as 25 minutes to return to normal, while in others the response was much more dramatic. The authors thought there were a number of possible explanations for raised cerebrospinal fluid pressure in pyogenic meningitis including occlusion of arachnoid granulations, generalised inflammatory brain oedema, basal occlusion of the subarachnoid spaces with the development of hydrocephalus, major seizures, and inappropriate antidiuretic hormone secretion. None of the children in this study died and there was no correlation between measured pressure and neurological outcome, although the median follow up was only 13 months.

The overriding concern with raised intracranial pressure is the formation of pressure cones, which are a common postmortem finding in acute bacterial meningitis[8] and may be the direct cause of death in as many as 30% of such children.[9] Coning may occur with protrusion of the cerebellar tonsils through the foramen magnum or the medial temporal lobe structures through the tentorial opening. There is a tendency for tentorial herniation to precede foramen magnum herniation but either may occur alone. The early symptoms and signs of cerebral herniation are similar to those of uncomplicated meningitis but often have a rapid onset and progression. There is progressive diminution in the level of consciousness, decorticate or decerebrate posturing, loss of doll's eye responses, pupillary abnormalities, tonic seizures, and respiratory abnormalities ranging through hyperventilation, bradypnoea, and periodic breathing to respiratory arrest. Unilateral herniation of one temporal lobe through the tentorial opening typically causes ipsilateral pupillary dilation and a contralateral hemiparesis. Symptoms and signs of coning occur in about 5% of cases of actue bacterial meningitis[10] and may recover particularly if prompt treatment is directed at controlling the underlying raised intracranial pressure with mannitol and passive hyperventilation.

Coning may occur in bacterial meningitis in the absence of lumbar puncture. Slack studied 88 of the 90 deaths from meningococcal infection in England and Wales in 1978 and reported coning in six,[11] one of whom had not had a lumbar puncture but died after a convulsion, an event known to increase intracranial pressure. However, the majority of meningitis patients who die as a result of a pressure cone do so within 24 hours of lumbar puncture. Some deteriorate immediately after the spinal fluid sampling but with many there is a delay of several hours suggesting that the amount of fluid removed may be less important than the continued leak of cerebrospinal fluid through the dural tear into the epidural space. Avoidance of lumbar puncture in children with suspected meningitis in whom there is clinical evidence of raised intracranial pressure or early coning would be expected to reduce the death rate, provided the lack of diagnostic accuracy (for example, type of organism and its antibiotic sensitivities) is not too high a price to pay. The question is how best to manage such children without resort to lumbar puncture.

Other conditions

In addition there are a few children with suspected meningitis and evidence of raised intracranial pressure who have some other condition which mimics meningitis clinically and which must be diagnosed promptly for optimal treatment. Posterior fossa tumours, acute hydrocephalus, cerebral abscesses, subdural haematoma bleeding from an arteriovenous malformation, meningoencephalitis, herpes simplex encephalitis, Reye's syndrome, and intracerebral haemorrhage may on occasions all present in a way that suggests acute bacterial meningitis with raised intracranial pressure. Lumbar puncture in many of these situations might be expected to carry a serious risk of coning. To illustrate this danger Richards and Towu-Aghantse described two patients who presented with impaired consciousness and neck stiffness and who were thought to have meningitis.[12] Both had symptoms of pressure coning after lumbar puncture. Subsequently computed tomography showed a subdural haematoma in one and a cerebellar haematoma in the other. Both patients subsequently died from what were potentially curable conditions.

Computed tomography

The Vancouver prospective study of computed tomography in acute bacterial meningitis in childhood showed that the initial scan obtained within 72 hours after admission was normal in the majority of the 41 children studied.[13 14] Abnormalities were noted in 14 children but were not specifically diagnostic of meningitis. Two children showed clear evidence of generalised cerebral oedema. Both had clinical evidence of raised intracranial pressure and subsequently died. Five children had focal low attenuation areas compatible with infarction and all had a hemiparesis on the opposite side. One child with pneumococcal meningitis showed obliteration of the basal cisterns consistent with the accumulation of pus. Eight children had evidence of subdural effusion but none of these were thought to be causing symptoms. Mild ventriculomegaly and widening of the subarachnoid spaces was a common finding in the second scan obtained 7–16 days after admission and was seen in 29 of the 35 children scanned at that time. None required shunting and the ventriculomegaly had reverted to normal in those children who had a third scan performed 5–23 months after admission. Contrast was not routinely given in this study. It is known that diffuse enhancement of the cerebral convexities and/or base of the brain may be seen after contrast if there is marked meningeal inflammation. Given the clinical context of suspected bacterial meningitis, such a finding on an enhanced computed tomogram would be virtually diagnostic. Unfortunately the finding is only seen in a small minority of children with acute bacterial meningitis at presentation.[15] Thus it must be concluded that computed tomography rarely gives specific positive information on which to make a diagnosis of acute bacterial meningitis.

On the other hand computed tomography is very helpful in excluding those conditions that may mimic bacterial meningitis with raised intracranial pressure. Posterior fossa tumours, acute hydrocephalus, cerebral abscess, and intracranial bleeds are all readily diagnosed on computed tomograms. Scanning may be less diagnostically helpful in Reye's syndrome, meningoencephalitis, and herpes simplex encephalitis where the findings may be non-specific or even normal.

Can computed tomography detect impending coning which is not apparent clinically? Unfortunately, the answer is probably not. Cerebral oedema may produce abnormalities on computed tomography including small lateral and third ventricles, generalised low attenuation of the white matter, and obliteration of the basal cisterns but there is considerable variation in ventricular and cisternal size which can make interpretation of a single scan unreliable in this respect.

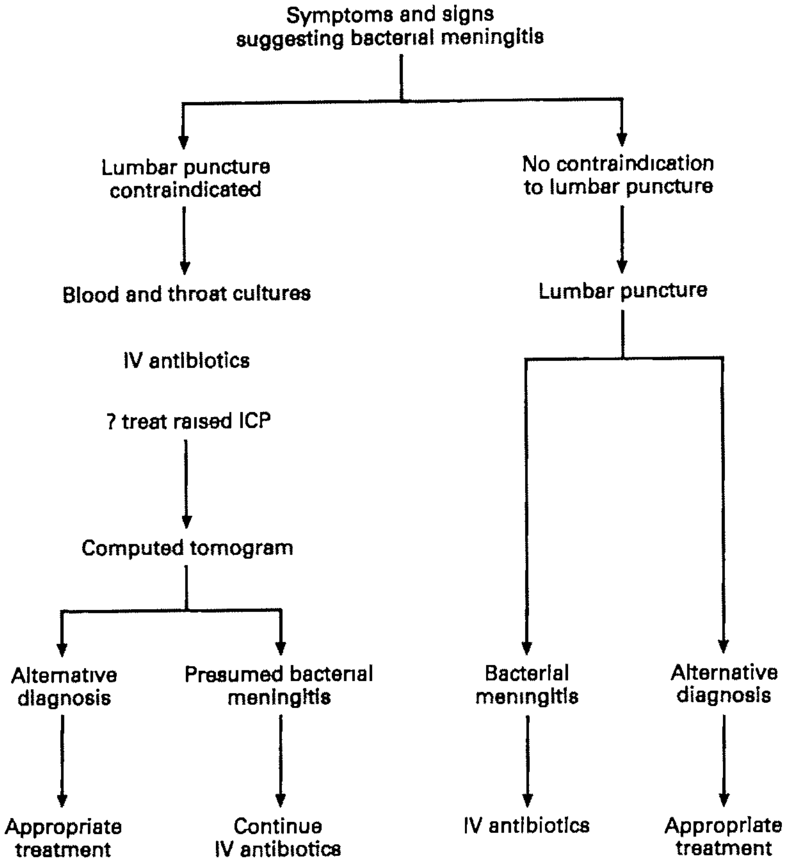
Practical solutions

Avoidance of lumbar puncture in children with suspected acute bacterial meningitis and evidence of raised intracranial pressure should reduce deaths from coning but we must be sure that such a policy does not lead to delayed antibiotic treatment. Clinical features suggesting dangerously elevated intracranial pressure and incipient coning are given in the table. Papilloedema is an uncommon finding in acute bacterial meningitis even when there is markedly raised intracranial pressure as it takes 24–48 hours for the discs to swell but its presence would be an absolute contraindication to lumbar puncture. The absence of papilloedema in this situation does not mean that lumbar puncture would always be safe and the other clinical features of raised intracranial pressure need to be taken into account. Most children with bacterial meningitis are drowsy but increasing coma suggests raised intracranial pressure. Convulsive seizures are not uncommon in the early stages of bacterial meningitis and do not in themselves signify raised intracranial pressure, but any convulsion is associated with a transient increase of pressure[16] and so lumbar puncture should not be done within 30 minutes after a short convulsive seizure or at all after a prolonged convulsion. Tonic seizures on the other hand may be a symptom of dangerously high intracranial pressure and lumbar puncture should not be carried out.[17] Septic shock would also be a contraindication, not because of raised pressure, but because the stress of the procedure itself may aggravate the cardiovascular collapse.

For these children immediate lumbar puncture is not carried out (see figure) but blood and throat cultures are taken before prompt instigation of appropriate intravenous antibiotic treatment.[18] Treatment for raised intracranial pressure may be required with intravenous mannitol, dexamethasone, and passive hyperventilation. Once the child's condition has stabilised, arrangements should be made for computed tomography. The main purpose of this is to exclude those conditions which may mimic acute bacterial meningitis. In bacterial meningitis the computed tomography may show non-specific changes but is unlikely to give proof of the diagnosis. The results of the blood cultures will become available in 24–48 hours and can be expected to identify the organism in about 90% of cases of

Contraindications to lumbar puncture in the child with suspected acute bacterial meningitis (see text for discussion)

Papilloedema
Coma
Hypertension
Bradycardia
Bradypnoea or irregular respirations
Fixed dilated or unequal pupils
Absent doll's eye movements
Recent or prolonged convulsive seizures
Tonic seizures
Decerebrate or decorticate posture
Hemiparesis
Septic shock



Flow diagram for management of the child with suspected acute bacterial meningitis. IV, intravenous; ICP, intracranial pressure.

Haemophilus influenzae or pneumococcal meningitis but only about 50% of cases of meningococal meningitis.[19] Failure to grow an organism means that the broad spectrum antibiotics must be continued for a full 10 days of treatment. After a day or two of treatment there may be the option of carrying out a delayed lumbar puncture if the contraindications are no longer present. This is rarely necessary but would allow cytological and chemical analysis of the cerebrospinal fluid with countercurrent immunoelectrophoresis for bacterial antigens if there is still serious doubt about the diagnosis.[20]

Fortunately the majority of children presenting with suspected acute bacterial meningitis have no contraindictions for lumbar puncture and this should be done promptly before starting intravenous antibiotic treatment. There is no place for routine computed tomography before or after lumbar puncture in the child with clinically uncomplicated acute bacterial meningitis.

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Sleep problems

Children's sleep disorders are common, often worrying, yet largely ignored in medical and other professional education with the risk that they may well be imprecisely diagnosed and inadequately treated.

The range of such disorders is much greater than might be supposed from textbook accounts. This is evident from the *International Classification of Sleep Disorders: Diagnostic and Coding Manual* which, although based largely on adult sleep disorders, contains descriptions of many problems encountered in babies, children, and adolescents.[1] Across this wide age range, sleeplessness of one type or another is probably the single most common sleep problem for which medical help is sought, and night time episodes of disturbed behaviour is possibly the next. Excessive daytime sleepiness is a less well appreciated symptom but one which involves an important and wide ranging differential diagnosis.

This annotation contains an outline of these main clinical sleep problems. Other important aspects of sleep in paediatrics, such as the interesting connections with physical growth,[2] are outside the scope of this article. Further details of children's sleep disorders are available in recent general accounts and the references to specific aspects that are provided.[3–5]

Sleeplessness

This term covers various problems especially settling difficulties, recurrent waking, early waking, and short duration sleep. The causes and approach required vary with age, for example, colic and long continued night feeding in babies; lack of bedtime routine or inappropriate daytime naps in young children; and bedtime fears, and other worries or emotional upset in older children and adolescents. Very frequent night waking and settling problems are described in a fifth of toddlers,[6] common causes being inappropriate bedtime procedures including inconsistency and inadvertent reinforcement of the troublesome behaviour. For such problems, behavioural treatments are relatively simple and effective[7] and more appropriate than hypnotic medication which is best reserved for short term use in crisis situations before other methods are introduced.[3] Training in such approaches needs to be more widely available to health visitors and others.

Night time attacks (parasomnias)

A major problem with recurrent episodes of disturbed behaviour appears to be the risk of misdiagnosis. Sometimes the term 'nightmare' is mistakenly used for any recurrent dramatic episode at night. In fact, the various forms of night time attack are different in their physiology and their management.[9] Timing of attacks usually gives a clue to their nature.

Headbanging and other *rhythmic movement disorders* are quite common at night in young children. They often occur at sleep onset, or on waking during the night, and seem to facilitate sleep. If they persist during the day they can be a feature of severe learning disability or psychosis but in the vast majority of usual cases there is no evidence of developmental disorder. Parents can be reassured that this strange behaviour is not of psycholcgical significance and that it will remit spontaneously by about 4 years of age. The same reassurance can be given in most cases of confusional arousals, night terrors, or sleepwalking. These '*arousal disorders*' which are often familial, arise in deep non-rapid eye movement (NREM) sleep and therefore mainly occur in the first third of the night when this type of sleep is most abundant. The child remains asleep during these episodes. True *nightmares* (frightening dreams) arise in rapid eye movement (REM) or dreaming sleep most of which occurs later in the night. The child is awakened by the frightening content of the dream and is able to describe its details. These various common forms of night time episode can be confused with *nocturnal seizures*,[10] which tend to occur at any time of night and have a very different significance, usually requiring physical investigation and treatment.

Non-epileptic night time attacks are usually 'developmental', that is, they remit spontaneously in time and are not usually associated with psychological disturbance. This may not be the case when attacks are very frequent, if they persist beyond the age they would normally cease, if they start beyond that age, or if they follow a traumatic event.

Excessive sleepiness during the day

This problem may not be brought to medical attention because of being misconstrued as laziness or 'opting out' of boring or difficult situations. Alternatively, parents and teachers may be concerned about learning and behaviour problems without realising that they are the result of hypersomnolence.

Most causes, especially in adolescence, are likely to be the result of habitual lack of sleep for social reasons; in other cases there is actual insomnia that is usually psychological in origin. A more specific cause can be identified in other children, such as obstructive sleep apnoea that is increasingly being recognised from before the age of 5 years.[11] Salient features include snoring or other breathing difficulties during sleep, restless sleep, and bedwetting. Obesity is not at all an invariable feature, indeed the growth of some children is retarded. Enlargement of tonsils and adenoids appears to be the most common cause of obstruction and their removal often improves daytime functioning including learning abilities and behaviour.[12] The narcolepsy syndrome can be difficult to detect early in its development; the sleepiness may well not be recognised as pathological, and early cataplexy and sleep paralysis may produce only subtle changes initially. Accompanying psychological problems can easily obscure or complicate the picture.[13]

Children at special risk of sleep disorder

Sleep disturbance can also significantly complicate physical and psychological disorders in children.[5] It can be caused in a variety of ways. Symptoms of *physical illness* may disrupt sleep or prevent its onset. Examples are painful or uncomfortable conditions (including middle ear disease that may well be overlooked) or where asthmatic attacks, seizures or nocturia repeatedly interrupt sleep. *Medication* is sometimes implicated such as antiasthma and some antiepilepsy drugs, as well as sedatives or hypnotics which can have paradoxical effects. Concern has been particularly expressed about the psychological and possibly physical effects of sleep deprivation in *intensive care units* caused by repeated procedures or by noise or other environmental factors. Sleep patterns may be seriously disturbed by the *stress* of the child's illness or being in hospital.

High rates of severe and persistent sleep disorder have been consistently described in children with a *learning disability*[14] causing considerable additional demands on parents and other carers. Sleeplessness is the most usual form of the problem but additional and more specific types of sleep disturbance are described in certain syndromes: obstructive sleep apnoea in Down's syndrome and most forms of mucopolysaccharidoses, and excessive sleepiness of uncertain origin in the Prader-Willi syndrome. Although there are relatively few research findings available, clinical experience indicates that certain *psychiatric disorders* are commonly associated with sleep disturbance, notably anxiety or depressive states, autism, and substance misuse.

Assessment

Clinical assessment of each child's recent sleep wake pattern needs to be comprehensive. A sleep diary kept by parents can be very instructive. Other relevant information may be contained in the medical history, findings on physical examination, and inquiries about the family circumstances and relationships.

A detailed clinical account and awareness of diagnostic possibilities is sufficient in most instances but, in selected cases, objective information from overnight video recordings or studies of sleep physiology will be required. The main conventional parameters for describing sleep structure are the electroencephalographram (EEG), electro-oculogram, and electromyogram. These measures permit NREM and REM sleep to be distinguished from each other and the EEG in particular allows NREM sleep to be graded into its four levels, the deepest levels usually being referred to as slow wave sleep. Overnight sleep consists of a series of NREM-REM cycles displayed diagramatically as a hypnogram.

Special sleep studies do not necessarily involve expensive inpatient sleep laboratory facilities. Home videos taken by parents themselves can be very instructive about children's night time attacks. Recordings of sleep physiology, also carried out in the child's home or other non-specialised setting, are now possible by means of portable cassette systems which provide detailed information on sleep staging and other objective aspects of sleep. Such procedures can be used where necessary to provide an objective check on the accuracy of reported symptoms, to define the sleep disorder precisely by demonstrating abnormal sleep physiology, and also to evaluate treatment objectively.

Treatments for sleep problems

These are many and varied and, of course, need to be chosen according to the nature and origin of the problem or factors maintaining it. In general, medication has been overemphasised in the past; it is often ineffective and can itself give rise to problems, especially disturbed behaviour. Explanation, reassurance, and support can have a major role in management especially in the case of developmental problems where parents may well overstate the significance of their child's symptom or behaviour. For example, showing them norms concerning children's sleep requirements at different ages can be very helpful. More specific practical advice may well be needed such as making the environment safe for sleepwalkers to prevent accidental injury, or not attempting to waken a child in the throes of a night terror as this will confuse and frighten the child, if successful.

In the case of chronic sleeplessness, it is not sufficient merely to reassure parents that the problem will resolve spontaneously because much harm can be caused in the meantime; the behavioural approaches mentioned earlier should be introduced. Several such approaches have been described mainly in the treatment of settling and night waking difficulties in toddlers. Each aims at changing the way parents deal with the problem. Those described by Douglas are: graded stages by which parents become less actively involved in getting the child to sleep; establishing a bedtime routine and teaching the child cues that it is time to go to bed and sleep; reinforcing settling and sleeping by means of rewards and incentives; and ignoring the difficult behaviour (an apparently quickly effective method but very difficult for many parents as the child may become so upset).[15] The choice of approach and the way it is implemented depends on the particular family. Different techniques may be needed in combination.

Other examples of specific measures include adenotonsillectomy in obstructive sleep apnoea, and adjustment of sleep disturbing treatment, wherever possible, for children with a physical illness. If inquiries reveal that the sleep problem is only one aspect of the child's psychiatric disorder, or of a complicated family situation, professional help from child psychiatry or psychology will be required.

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Routine discharge examination of babies: is it necessary?

The neonatal examination is an integral part of child health surveillance.[1] A thorough physical examination can be regarded as a screening procedure to check that the baby is normal, to look for congenital abnormalities, and as a reassurance for parents. The contact also offers an excellent opportunity for parents to ask questions, and for health promotion including especially a discussion on feeding practices, immunisation, and reducing the risks of sudden infant death.

First neonatal examination

The first full neonatal examination has a high yield of abnormalities and is widely accepted as good practice. This was confirmed by Moss *et al* in an audit of 1795 examinations in which the initial examination succeeded in detecting abnormalities in 8·8% of infants, orthopaedic problems being the most common.[2] This examination is generally recommended to be conducted within 24 hours of birth.[3] This has, however, been questioned by Hughes *et al* who showed that a single late examination, 24 hours before discharge, yielded as many abnormalities as two (early and late) neonatal examinations.[4] They argue that as most major visible abnormalities will be detected by the midwife or parents very soon after birth, the examination can be delayed until 24 hours before discharge, when management problems may have become apparent. This ignores the parental reassurance value of an early examination, but indicates that a less rigid attitude to timing can be adopted. This approach would also ease the problem of routine examinations over a weekend when medical staffing can be difficult.

Discharge examination

The Maternity Services Advisory Committee recommended a routine neonatal discharge examination in 1985.[3] However, this has not been generally accepted and the 1989 report of the Joint Working Party on Child Health Surveillance recommended only a repeat examination of hip stability on discharge or within 10 days after birth.[1] This altered recommendation was partly a response to the welcome trend towards early discharge which makes it increasingly difficult to ensure that a second examination is carried out. Moss *et al* addressed this problem with an audit assessing the value of the second neonatal examination.[2] The examination, performed on 97·3% of 1795 newborn infants, was done on the day of discharge on 1428 infants (79·6%). Because of early discharge, 38·5% of babies were examined on or before day 2, the median time of the discharge examination being 4 days of age. The second examination uncovered previously undetected problems in 63 infants (3·6%). However, 49 abnormalities were minor, such as superficial infection and jaundice not requiring phototherapy; in seven babies the abnormality was not new and should have been detected by the first examination. Only seven infants had a new or potentially important abnormality: jaundice, a transient heart murmur, a distended abdomen which resolved spontaneously, and—most significantly—dislocatable hips in four infants. An important finding was therefore detected in only 0·5% of second examinations. The study concluded that a full second examination cannot be justified, but a test for hip stability should be performed.

The Hall report discusses the key role of parents in the detection of defects but stresses that some defects are unlikely to be recognised even by the most astute parents and require a special search by health professionals.[1] In this category congenital dislocation of the hip and congenital heart disease require special consideration.

CONGENITAL DISLOCATION OF THE HIPS

The current screening programme for congenital dislocation of the hip was set out in 1986[5] and endorsed in the Hall report. But it has been criticised because of poor specificity and sensitivity.[6–8] The screening programme been thoroughly evaluated by Dunn *et al*.[9] In a cohort of 23 002 infants, 445 (1·9%) were diagnosed as having dislocated hips. In 33% the abnormality was detected at the initial examination on the first day, but in 17% the instability was not found until the discharge examination that was performed at a mean of 5 days. Thus 0·3% of discharge examinations detected an unstable hip, a rate similar to that found by Moss *et al*. It is not clear why these were not detected at the first examination; perhaps signs of instability can be temporarily lost shortly after birth[5] or, as seems more likely, the signs were missed.

CONGENITAL HEART DISEASE

The Hall report makes no recommendation for a second neonatal examination to detect congenital heart disease. Moss *et al* found no congenital heart abnormality at the second examination, although it has been pointed out that this audit was not large enough to encounter many important abnormalities, such as coarctation of the aorta, which are potentially detectable.[10] Further information is from an unpublished audit from the database of the cardiology unit at Bristol Children's Hospital (R Martin, personal communication). The neonatal notes of 50 children with congenital heart disease were scrutinised. In only 20 was the abnormality detected in the newborn period. In one this was prompted by an abnormal antenatal scan, in seven symptoms and in a further five during surveillance on the neonatal unit for other reasons. In only seven infants was the abnormality picked up by routine examination—the first examination in six and the second in one. Both cases of coarctation of the aorta were missed. The discharge examination as it is currently performed is therefore seriously deficient as a good screening test for congenital heart disease.

Conclusion

The routine discharge examination as currently performed is at best a test of hip stability and an opportunity to talk to the mother about her baby. The detection rate for other abnormalities is disappointingly low, and probably due to the examination being performed too soon after the first full examination. There is also the recommendation that the test of hip stability shortly after birth should not be duplicated for fear of damaging the joint.[5] The move toward earlier discharge means that in 38·5% of infants the test is duplicated within two days of delivery.

I consider that a second neonatal examination could be made useful if its timing is changed and aims more clearly defined. Rather than at discharge, with its very variable timing, the examination should be performed at 7 to 10 days of life with the clearly defined aims of detecting unstable hips, congenital heart disease, and late onset or progressive jaundice. This would be performed in most instances by the general practitioner as part of the child health surveillance programme; for infants remaining in hospital, paediatric staff would be responsible. As with all aspects of child health surveillance, this policy must be regularly reviewed.

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ORIGINAL ARTICLES

Do maternal and intrauterine factors influence blood pressure in childhood?

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Abstract

It has been proposed that maternal health and nutrition may be important in the development of adult cardiovascular risk, and that blood pressure may be an important intermediate step in this process. To examine the relevance of this hypothesis in contemporary British children, the relationships of several maternal factors to blood pressure were studied in 3360 children of European origin aged 5–7 years. Maternal age, height, and body mass index were all positively related to blood pressure in childhood but these relationships were abolished once the child's body build was taken into account. Maternal social class, educational attainment, and history of smoking in pregnancy showed no relationship with blood pressure in childhood. Parity showed an inverse association with blood pressure, but this appeared to be due to an association between total sibship size and blood pressure, suggesting a postnatal rather than a prenatal origin. Blood pressure was higher in children whose mothers had a history of high blood pressure but this association was no stronger than that for paternal history. Both birth weight and gestational age were inversely related to blood pressure at 5–7 years. The association between birth weight and blood pressure was attenuated by standardisation for gestational age, and the relationships between birth weight and blood pressure were similar in preterm and full term infants.

No specific associations between blood pressure and the maternal factors studied have been observed in this population. Hypotheses relating maternal factors to cardiovascular risk need to specify the timing and nature of their effects more precisely. Although the relationship between birth weight and blood pressure is not fully understood, it appears to reflect size at birth rather than fetal growth rate.

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Barker has argued that factors acting in early life may be important in the development of hypertension and cardiovascular disease in adult life.[1] The environment in fetal and infant life, which is strongly influenced by maternal health and especially by maternal nutrition, may be particularly important.[1 2] While the links between fetal and infant experience and adult cardiovascular risk are incompletely understood, it has been suggested that failure of fetal growth may play an important part.[1] The demonstration of an inverse association between birth weight and blood pressure both in childhood[3–7] and in adults[6 8 9] has suggested that blood pressure is likely to be an important link between early influences and later cardiovascular risk. It has been postulated that this hypothesis may account for both the secular trends in cardiovascular disease observed in Great Britain over the past 50 years[10] and for the current patterns of geographical variation in cardiovascular mortality.[11–12] As the public health implications of the hypothesis principally concern the health and nutrition of mothers and their infants, it is important to understand the extent to which these early influences are relevant in the present generation of children.

In this report, two aspects of the hypothesis are examined in a contemporary group of children. The first is the relationship between indicators of maternal health (particularly those related to maternal nutrition) and blood pressure in childhood. The indicators of maternal health considered include age, height and body mass index, social factors (including social class, age of completion of full time education), smoking in pregnancy, parity, and a history of high blood pressure. Among these, maternal height is likely to reflect childhood influences,[13] including nutrition,[14] while maternal social factors are strongly related to dietary intake of both macronutrients and micronutrients during pregnancy.[15] The second aspect of the hypothesis examined is the relation between birth weight and blood pressure and, in particular, the suggestion[6 8 9] that fetal growth rate may play a central part in this relationship.

Subjects and methods

SAMPLING PROCEDURES

The study was carried out in 10 towns in England and Wales, five with exceptionally high adult cardiovascular mortality rates (Wigan, Burnley, Rochdale, Port Talbot, and Rhondda) and five with exceptionally low cardiovascular mortality rates (Esher, Leatherhead, Chelmsford, Bath, and Tunbridge Wells). The selection of these towns has been described in detail elsewhere.[16] Within each town, a sample of 10 primary schools, stratified by religious denomination and, in the case of county primary schools, by size and location, was selected. Any school unable to take part was replaced by the school matching most closely in denomination, size, and location. Within each school, two classes of children aged between 5·0 and 7·5 years were randomly selected to provide a sample of 50–60 children who were invited to participate. The validation of this sampling method has been described.[17]

SURVEY PROCEDURES

All measurements were made between January and July 1990 by a team of four trained nurse observers working in pairs. Standardised procedures were used throughout. Children, in groups of four, rested for a period of at least 5 minutes before the measurements described below were carried out, with subjects dressed in light clothing without shoes. *Height* was measured to the last complete millimetre using either a Holtain electronic stadiometer or a CMS portable stadiometer. *Weight* was measured to the last complete 0·1 kg with a Soehnle digital electronic weighing scale. *Blood pressure* was measured with the child seated and the arm supported at chest level. Two blood pressure measurements were made 1 minute apart in the right arm, using the Dinamap 1846SX automated oscillometric blood pressure recorder (Critikon).[18 19] All measurements were made with the child cuff size (bladder dimensions 15·5×8 cm), ensuring that the cuff width to arm circumference ratio of 40–50% recommended by the American Heart Association[20] was met for 79% of the study population. *Ethnic group* was assessed on the basis of the child's appearance.

QUESTIONNAIRE

A self administered questionnaire sent to the parents of all participants on the day of examination was used to provide information on maternal and intrauterine factors. *Maternal age* was determined from the mother's year of birth, and refers to her age at the time of the child's birth. *Maternal weight and height* were recorded. *Maternal social class* was determined from the mother's present or most recent occupation, classified using the 1980 manual of the Office of Population Censuses and Surveys. *Maternal education* was assessed by asking the age at which full time education had been completed. *Cigarette smoking in pregnancy*, including the number of cigarettes smoked, was recorded. Mothers were asked to record the dates of birth of all older and younger siblings of the child examined; the number of older children formed the basis for assessment of parity. Inquiry was made as to whether mothers had ever had their blood pressure measured, and whether they had ever been told that their blood pressure was high. A similar question was asked of fathers. Mothers were asked to record *birth weight* as accurately as possible. Whether the delivery was early or late and, if so, by how many weeks, was used to determine *gestational age*.

STATISTICAL METHODS

Age, height, and body mass index in mothers, and gestational age and birth weight in children, have been treated as continuous variables in regression analyses, but have been grouped in fifths for presentation in figures and tables. Age, height, body mass index, and blood pressure in children have been treated as continuous variables. Maternal social class and age of completion of education have been treated as class variables; the significance of relationships with blood pressure has been based on tests for linear trend. The number of older siblings (parity) and younger siblings has also been treated as class variables; older sibling numbers of three or more and younger sibling numbers of two or more have been grouped throughout. Cigarette smoking in pregnancy and parental history of high blood pressure have been treated as 0/1 variables. All results have been standardised for small differences in blood pressure measurement between observers. In this study population age, sex, height, and body mass index were all independently related to blood pressure. Standardisation for age, sex and, where appropriate, height or body mass index or both, have been carried out using standard linear regression techniques.

Results

The results are based on 3360 European children (67% response rate) who both took part in the measurement survey and for whom parental questionnaires were returned. Analyses of maternal factors have been restricted to children living with their natural mothers (n=3307); analyses of intrauterine factors are restricted to singleton births (n=3259). Analyses of parental history of high blood pressure have been restricted to those subjects whose parents reported having had a blood pressure measurement made at some time (3215 mothers, 2310 fathers). Results are presented for systolic pressure throughout. Relationships for diastolic pressure are consistent with, but weaker than, those for systolic.

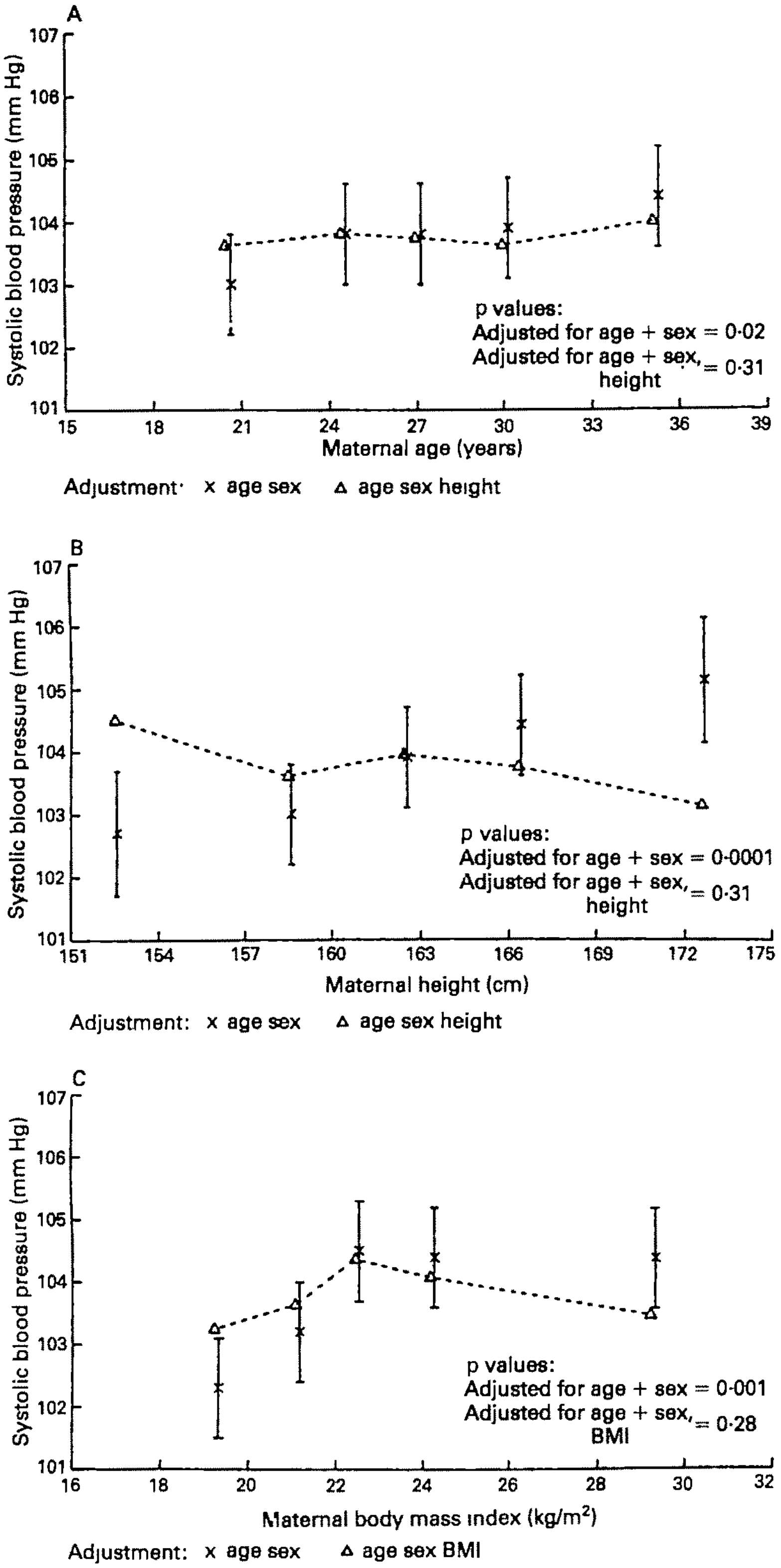
MATERNAL FACTORS FOR BLOOD PRESSURE

Maternal age, height, and body mass index

The relationships between maternal age, height, and body mass index and systolic blood pressure in children are presented in the figure. In a model standardised only for age and sex, all three variables show strongly positive, and statistically significant, associations with systolic blood pressure, which are largely independent of one another. However, in these children, height is correlated both with maternal age (r=0·13) and with maternal height (r=0·33) while body mass index is correlated with maternal body mass index (r=0·18); both of these factors are strongly associated with blood pressure in childhood. When the relationships between maternal age and blood pressure and maternal height and blood pressure are standardised for the effect of the child's height (in addition to age and sex), these associations are effectively abolished (figure). Similarly, when the relationship between maternal body mass index and blood pressure is standardised for the effect of the child's body mass index, this association is also removed (figure).

Maternal social factors, smoking in pregnancy, parity and blood pressure

The relationships between maternal social class, age at completion of full time education and smoking in pregnancy are presented in table 1. Neither maternal social class nor age at



(A) Maternal age, (B) height, (C) body mass index (BMI), and systolic blood pressure in children. Results are mean and 95% confidence intervals

Table 1 Maternal factors and systolic blood pressure in children

	No of children	*Systolic blood pressure (mm Hg)*	
Maternal social class·			
I	37	106·1 (1·7)	
II	717	103·8 (0·4)	
IIINM	1143	104·3 (0·3)	
IIIM	240	104·1 (0·7)	
IV	655	103·4 (0·4)	Test for trend
V	150	104·1 (0·9)	p=0·30
Maternal full time education completed			
≤16 years	1863	103·7 (0·3)	
17–20 years	890	104·4 (0·4)	Test for trend
21 years +	439	103·6 (0·5)	p=0·62
Maternal smoking in pregnancy			
Yes	870	103·5 (0·2)	Test for difference
No	2390	104·0 (0·4)	p=0·29
Parity.			
0	1534	104·5 (0·3)	
1	1131	103·4 (0·3)	
2	415	102·4 (0·5)	Test for trend
3+	154	103·5 (0·9)	p=0·001
Maternal history of high blood pressure:			
Yes	1167	105·0 (0·3)	Test for difference
No	2048	103·1 (0·2)	p<0·0001
Paternal history of high blood pressure			
Yes	288	106·0 (0·6)	Test for difference
No	2022	103·8 (0·2)	p=0·001

Figures are means (SE) All analyses are standardised for age and sex. Analyses are based on 3307 subjects with natural mothers, for whom a social class could be allocated in 2942, a level of educational attainment in 3192, a smoking status in pregnancy in 3260, and a parity in 3234 Analyses of parental history of high blood pressure are restricted to 3215 mothers and 2310 fathers who reported having had their blood pressure measured

completion of full time education showed a consistent relationship with blood pressure in childhood, a finding which is unchanged by using the same measures for the father or head of household (data not presented). Maternal smoking in pregnancy also shows no relationship to blood pressure in childhood. Parity, in contrast, shows an inverse, graded relationship with blood pressure, which is consistent in all groups except the small 3+ group (table 1). Firstborn children have mean systolic pressures 2·1 mm Hg higher than those whose mothers were parity 2. It is important, however, to consider whether this association is really dependent on parity, or whether it reflects the number of older siblings on which the measure of parity is based. One way of approaching this question is to examine whether there is any relationship between the number of younger siblings and blood pressure. This relationship is examined for each number of older siblings in the columns of table 2. Mean blood pressure tends to fall with increasing numbers of younger siblings; the effect is most consistent in the largest cells, towards the top, left hand corner of the table.

To assess the strength of the independent relationships between younger sibling numbers, older sibling numbers and blood pressure, a multiple linear regression analysis including the two factors, together with age and sex, was carried out. The linear regression coefficients (representing the difference in systolic blood pressure for a single change in sibling numbers) are very similar both for older siblings (−1·11 mm Hg; SE 0·24 mm Hg) and for younger siblings (−1·29 mm Hg; SE 0·30 mm Hg). Results are also consistent for diastolic pressure. These findings suggest that the associations are dependent on the total number of siblings, rather than on parity. As numbers of both younger and older siblings are related to blood pressure levels in childhood, this association is likely to reflect a postnatal, rather than a prenatal, effect.

Maternal history of high blood pressure

Table 1 presents the relationship between a

Table 2 Older siblings, younger siblings, and systolic blood pressure

		Older siblings			
		0	*1*	*2*	*3+*
Younger siblings	0	105 4 (0·5)	104 3 (0 4)	103·2 (0 6)	104 7 (1 0)
	1	104 3 (0·4)	101 4 (0 6)	99 7 (1 2)	99 6 (2 1)
	2+	103·8 (0·7)	101 9 (1·4)	101·5 (2 8)	102 6 (4 0)

Figures are mean (SE systolic blood pressures (mm Hg) Analyses are standardised for age and sex and are based on 3234 subjects with complete data on older and younger siblings.

maternal history of high blood pressure and childhood blood pressure. Mean blood pressure levels are significantly higher in subjects with a maternal history of high blood pressure than in those without. Whether or not maternal high blood pressure was observed during the pregnancy of the child examined, makes little difference to the outcome (data not presented). The overall differences in systolic blood pressure, however, between mothers with and without a history of high blood pressure (1·9 mm Hg, 95% confidence intervals 1·1 to 2·7 mm Hg) are very similar to those for a paternal history of high blood pressure (2·2 mm Hg, 95% confidence intervals 0·9 to 3·5 mm Hg).

BIRTH WEIGHT, GESTATIONAL AGE, AND BLOOD PRESSURE

To examine the relationships between birth weight, gestational age, and blood pressure in childhood, it is necessary to standardise results, not only for age and sex, but also for current body build.[7] In this study population, height is correlated both with birth weight (r=0·18) and to a lesser extent gestational age (r=0·05); similar associations are also observed for body mass index (r=0·21 and r=0·05 respectively). Table 3 presents the relationships between birth weight, gestational age and blood pressure, standardised for height and body mass index. Both of these factors show highly significant inverse relationships with systolic blood pressure. There is a mean difference in systolic blood pressure of 2·7 mm Hg between the highest and lowest birthweight groups and a mean difference of 4·3 mm Hg between children born at 28–30 weeks and those born at 40–42 weeks. These relationships are not affected by adjustment for parity or number of siblings, or by adjustment for parental history of high blood pressure.

Table 3 Birth weight, gestational age, and systolic blood pressure

	No of children	*Systolic blood pressure (mm Hg)*
Birth weight (g)		
765–2950	659	104·7 (0·4)
2951–3230	633	104·7 (0 4)
3231–3460	608	104 3 (0·4)
3461–3740	683	103 5 (0 4)
3741–4880	603	102 0 (0 4)
p value (linear regression)		<0·0001
Gestational age (weeks)		
28–30	13	107·8 (2 7)
31–33	23	105 5 (2·0)
34–36	114	104 0 (0 9)
37–39	757	104·6 (0 4)
40–42	2105	103·4 (0 2)
43–44	47	104·5 (1·4)
p value (linear regression)		<0 0001

Figures are mean (SE) Analyses are standardised for age, sex, height, and body mass index and are based on 3259 singleton births, of whom birth weights are available for 3186 subjects and gestational age for 3061 subjects

Table 4 Birth weight, gestational age, and systolic blood pressure

	Systolic blood pressure (mm Hg)			
	r	*SE*	*t*	*p*
Separate analyses:				
Birth weight	−2·05	0 33	−6 16	<0 0001
Gestational age	−0 35	0 09	−3 95	<0 0001
Multiple regression analyses				
Birth weight	−1 90	0 42	−4 54	<0 0001
Gestational age	−0 06	0 11	−0 57	0 57

Units of regression coefficients are mm Hg/kg or mm Hg/week throughout All analyses are standardised for age, sex height, and body mass index and are based on 3061 subjects with complete data on birth weight and gestational age.

Other investigators examining the association between birth weight and blood pressure have suggested that fetal growth rate may play an important part.[8,9] To examine the extent to which fetal growth rate is responsible for the relationship between birth weight and blood pressure, the relationship has been examined separately in preterm births (36 weeks or earlier) and term births (37 weeks or later). The rationale for such an analysis is that whereas variation in birth weight in preterm infants is strongly related to variation in gestational age (r^2=0·49), variation in birth weight at term, although still related to gestational age, is much less strongly so (r^2=0·10). Variation in fetal growth rate therefore plays a more important part in variation in birth weight at term than in preterm infants. If the association between birth weight and blood pressure is explained by fetal growth rate, it would be expected that the relation between birth weight and blood pressure would be stronger in term births than preterm births. However, the coefficients for the regression of systolic blood pressure on birth weight are very similar in preterm infants (−1·84 mm Hg/kg, 95% confidence interval −0·38 to −3·30 mm Hg) and in term infants (−2·06 mm Hg/kg, 95% confidence interval −1·22 to −2·90 mm Hg). These results provide no strong evidence of a difference in regression slopes between preterm and term infants for systolic pressure (p=0·80); a similar pattern is seen for diastolic pressure (p=0·57).

A more precise method of examining the importance of fetal growth rate is to examine whether standardisation of the relation between birth weight and blood pressure, for the effect of gestational age, increases the strength of the relationship (table 4). Standardisation for gestational age weakens, not strengthens, the association between birth weight and systolic blood pressure, while the association between gestational age and blood pressure disappears. These results suggest that birth weight, rather than a measure of fetal growth rate, is the factor most importantly related to blood pressure in this context.

Discussion

This study has examined the relationship between a group of maternal and intrauterine factors and blood pressure in a population of children from 10 towns in England and Wales with widely differing adult cardiovascular mortality rates. Although maternal age, height, and body mass index were related to blood pressure, none of these remained so after standardisation for current body build of the child. Neither maternal social class, educational attainment, nor smoking in pregnancy showed any relationship with blood pressure in childhood. Parity (based on the number of older siblings) was inversely related to blood pressure. The number of younger siblings showed an inverse association of similar strength, suggesting that number of siblings, rather than parity, was the important factor in this context. While a maternal history of high blood pressure was associated with a higher blood pressure level in childhood, the strength of this association was no greater than that for a paternal history of high blood pressure. Both birth weight and gestational age were inversely related to blood pressure once the effect of current body build was taken into account. The association between birth weight and blood pressure was similar for preterm and term infants. Moreover, standardisation for gestational age did not appear to increase the strength of the association between birth weight and blood pressure.

MATERNAL FACTORS AND CHILDHOOD BLOOD PRESSURE

Relationships between maternal factors and childhood blood pressure have been examined in several previous studies. Weak associations between maternal age and blood pressure have been described in an earlier study of 5–7 year olds[7] and in a study of 0–20 year olds.[21] No important association between maternal height and blood pressure in 10 year olds was observed in the 1970 British Births Survey.[6] In the present study, the effects of maternal age and height were abolished by adjustment for childhood height, while the effect of maternal body mass index was abolished by adjustment for childhood body mass index. The precise reason for these observations in uncertain. One possibility is that the associations between these maternal factors and blood pressure are confounded by childhood body size, and that they are of no importance. A second possibility is that childhood body build represents an intermediate step on a causal pathway relating maternal factors and childhood blood pressure. The results of our study do not allow us to distinguish between these possibilities. However, we have also examined the associations between paternal age, height, and body mass index and childhood blood pressure, which are very similar to those for maternal factors (data not presented). Thus, even if these maternal factors are related to childhood blood pressure, the results do not provide strong evidence for a specific maternal effect rather than a general parental effect.

No consistent relationship was observed between maternal social factors and blood pressure at 5–7 years. While several studies have provided evidence of a relationship between social class and blood pressure in British adults, with lower mean blood pressures in non-manual occupational groups,[22 23] few studies have reported a relationship between social class and blood pressure in British children. Beresford and Holland observed a 4 mm Hg gradient in systolic pressure across paternal social class groups in 472 children aged 5–8 years,[24] and Law *et al* recently reported that blood pressures were lower in social classes I and II in 405 children aged 4 years.[25] Both our present study and an earlier study in 5–7 year olds failed to demonstrate an association between maternal social factors and blood pressure.[7] The absence of associations in these studies is not simply due to the use of specifically maternal measures of social class (rather than one based on paternal social class), or to the use of a specifically occupational measure of social class (rather than one based on housing tenure or car ownership). These findings are consistent with those of MacIntyre and West, who observed that the absence of an association between social class and blood pressure in adolescents was not simply an artefact resulting from the use of an occupational social class measure.[26]

The inverse relationships between numbers of older siblings, numbers of young siblings and blood pressure are broadly consistent with the findings of our earlier study.[7] Other investigators, however, have not confirmed this observation,[21 25] although an association between the absence of siblings and high blood pressure has recently been reported in adults.[27] The association between older sibling numbers and childhood blood pressure could, in theory, be explained by a prenatal, maternal effect related to parity. However, the findings of the present study (suggesting that associations both older and younger sibling numbers are equally strongly related to childhood blood pressure) strongly imply that the association is likely to be postnatal and that a specific maternal effect is unlikely.

The assessment of parental blood pressure status is based on an extremely crude measures The association between a maternal history of high blood pressure and blood pressure in childhood is consistent with earlier reports based on direct measurement of maternal blood pressure.[24 25] In this study, the association between a maternal history of high blood pressure and childhood blood pressure was of a similar strength to that of paternal history. As both of these parental measures are equally crude, this comparison should be valid even if weak. Moreover, the findings are consistent with the results of earlier studies, based on measurement of parental blood pressures, which observed associations with childhood blood pressure which were of similar strength for both maternal and paternal influences.[24 28] Although one recent study has suggested that maternal blood pressure may be more important than paternal blood pressure,[25] the differences between maternal and paternal relationships in that study did not approach statistical significance. Strong support for a specific association between the blood pressures of mothers and their offspring, independent of that observed for fathers, appears to be lacking at present.

BIRTH WEIGHT, GESTATIONAL AGE, AND BLOOD PRESSURE

Several studies have observed inverse associations between birth weight and blood pressure, both in childhood[3-7] and in adulthood,[6 8 9] although this has not been a universal finding.[29] The magnitude of the association observed in this study is similar to that of our earlier study[7] and that of Law *et al* in 4 year olds[25] but stronger than that reported in 10 year olds from the 1970 British Births Survey.[6] This discrepancy may be explained by the large number of observers and the rounding of blood pressure values in the latter study. In the British Births Survey, no association between gestational age and blood pressure was observed. However, the effect of standardisation for current body build, as used in the current study, was not described, however.

IMPLICATIONS FOR HYPOTHESES EMPHASISING THE IMPORTANCE OF EARLY LIFE INFLUENCES IN THE DEVELOPMENT OF ADULT CARDIOVASCULAR DISEASE

Maternal factors

No evidence has been observed in this study population to suggest the presence of specific relationships between maternal factors and blood pressure in childhood. These findings do not invalidate the general hypothesis that early influences, particulary maternal influences, may affect the risk of cardiovascular disease. The maternal measures reported here are possibly too crude, although the range of maternal heights and social circumstances is wide, despite the absence of children from inner cities in the sample. Blood pressure is possibly not the important mechanism relating maternal influences to adult cardiovascular risk; other pathways, including impaired glucose tolerance, have recently been suggested.[2 30] It is also conceivable that early influences act by long term programming[2] and therefore, no appreciable effects on blood pressure are to be expected in childhood The findings emphasise that the study of early influences on cardiovascular risk in the present generation of children requires the development of more specific hypotheses for testing. In particular, the maternal factors that are important, and the nature and timing of their influence on offspring, need to be specified with greater precision. One example of this greater specificity has been the recent suggestion that maternal anaemia may be related to blood pressure in offspring.[25] Although preliminary results are encouraging,[25] however, the hypothesis requires further exploration and substantiation.

Table 5 Studies relating weight and blood pressure at birth

Author	*Reference*	*No of subjects*	*Association*
Term infants*			
Moss et al	31	74	Positive
Kitterman *et al*	32	45	Positive
Lee *et al*	33	257	Positive
Schachter *et al*	34	392	None
de Swiet *et al*	35	1740	Positive
Preterm infants			
Holland and Young	36	15	Positive
Goodman *et al*	37	28	Positive
Moss *et al*	31	26	Positive
Levison *et al*	38	21	Positive
Low birthweight infants			
Versmold *et al*	39	16	Positive

*Studies included in this list include those in which blood pressures were measured within seven days of birth

Birth weight and blood pressure

In the earlier descriptions of the inverse relationship between birth weight and subsequent blood pressure, two general explanations for the associations have been put forward. Some authors have suggested that the relationship reflects a direct effect of intrauterine factors on the developing fetal cardiovascular system[8 9] whereas others have suggested that the relationship is essentially due to the postnatal sequelae of low birth weight, particularly rapid postnatal growth (catch-up growth).[5] Explanations in the first group include the suggestion of Gennser *et al* that the placental changes in intrauterine growth retardation lead to resetting of blood pressure regulation[8] and Barker *et al's* suggestion that the processes responsible for fetal growth retardation may result in long term changes in arterial structure and compliance.[9] The first of these explanations implies that blood pressure in low birth weight infants is likely to be higher by the time of birth. Those studies, however, that have measured blood pressure at, or shortly after, birth have generally observed a positive, not an inverse, relation between weight and blood pressure at that time (table 5), which argues strongly against the suggestion of Gennser *et al*. A common feature of both the intrauterine explanations is the importance accorded to retardation of intrauterine growth. The analyses described in this report have examined the possibility that fetal growth rate, rather than birth weight, is related to blood pressure. First, the relationship between birth weight and blood pressure has been examined in preterm and term infants, in which the contribution of fetal growth rate to differences in birth weight differs. Second, the effect of standardisation for gestational age on the relationship between birth weight and blood pressure has been examined. The results of both analyses suggest that birth weight, rather than birth weight for gestational age (a measure of fetal growth rate) is important. Interpretation of these findings must be cautious, first because birth weight and gestational age are strongly correlated ($r=0\cdot58$) and also because measurement of gestational age is liable to error, more so when based on recall after several years. A comparison of gestational age data collected by maternal recall at 9–11 years in 851 subjects shows a high level of agreement with data from birth records (mean difference 0·20 weeks, SD 1·3 weeks) (PH Whincup, unpublished data). Moreover, the demonstration of a relationship between birth weight and recalled gestational age again suggests that the gestational age data are at least partially valid. The results, therefore, provide no support for the earlier contention that fetal growth rate is important in explaining the association between birth weight and blood pressure.[8 9] The biological significance of the observations remains uncertain, however. The findings do not resolve the question of whether the explanation for the association is prenatal or postnatal. They suggest that, if prenatal, the explanation must account for a relationship that is similar both in prematurity and growth retardation, conditions that are distinct in many aspects of their aetiology[40] and clinical features.[41] If the explanation is a postnatal one, the observations also cast uncertainty on the importance of early catch-up growth,[5] which is more marked in preterm infants than in those with intrauterine growth retardation.[42]

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Management and outcome of severe head injuries in the Trent region 1985–90

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Abstract

In a five year period, 39 children (29 boys, 10 girls) aged 2 months to 13 years (mean 7·8 years) were studied who had suffered a major head injury (29 road traffic accidents, six falls, and four non-accidental injury). The injury had been assessed clinically and by cranial computed tomography or cranial ultrasound (in a single baby of 2 months). Initial Glasgow coma scores for all subjects ranged from 3–11 (mean 5·5), intact survivors 5–11 (7·4), minor handicap 4–11 (5·1), major handicap 3–6 (4·3), fatalities 3–6 (4·1). All were treated with sedation, paralysis, hyperventilation (arterial carbon dioxide tension 3·0–3·5 kPa), intracranial pressure monitoring and moderate body surface hypothermia to 32°C. Nine children died and 30 survived (nine intact, 13 minor disability, and eight major disability). The worst cerebral perfusion pressure was over 40 mm Hg in all but one survivor, and less than 40 mm Hg in seven of nine fatalities. Severe hypocapnia both in the first 24 hours and overall was correlated with poor outcomes (dead or major disability), as were bilateral contusions or diffuse axonal injury.

(*Arch Dis Child* 1992;67:1430–5)

There is some evidence that control of raised intracranial pressure after major head injury can reduce mortality and improve the quality of survival.[1–4] Most treatment protocols advocate hyperventilation to reduce arterial carbon dioxide tension (PaCO_2), sedation with opioids and benzodiazepines, and in resistant cases barbiturate administration to reduce cerebral metabolism and to control intracranial pressure and maintain cerebral perfusion pressure (mean arterial pressure less intracranial pressure) above 50 mm Hg when possible and always above 40 mm Hg.[5–7] However, with barbiturate coma estimation of brain death is invalidated. Consequently, we have managed seriously head injured children without barbiturate coma but in substitution have used body surface cooling using a cooling mattress to bring the surface temperature down to 32°C, thereby enabling greater control of intracranial pressure.

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Subjects and methods

Thirty nine children (29 boys, 10 girls), aged 2 months to 13 years (7·8 years) were treated. The children presented in the Trent region over 1985–90 with major head injuries that resulted from road traffic accidents in 29 (25 as cyclist or pedestrians and four within cars), from falls in six, and non-accidental injury in four. The Glasgow coma scale scores at presentation varied from 3–11 (mean 5·5), and are related to final outcomes in table 1. All were thought clinically to be showing signs of raised intracranial pressure. One baby of 2 months had an extracerebral collection noted on ultrasound. One patient had extensive calvarial fractures with cranial sutural diastasis and subluxation of the cervical spine, and thus was not scanned. The remaining 37 had cranial computed tomograms, and of these 36 were reported as abnormal. A retrospective analysis of 32 of these 37 scans was performed by two radiologists (TJ and AET) who were not given the patient outcomes, to look for features on these scans that might predict adverse outcome, and were then correlated to the actual outcomes. The scans of five patients were untraceable.

The patients were all treated at the Queen's Medical Centre children's intensive care unit.

The treatment protocol included hyperventilation aiming for a PaCO_2 of 3·0–3·5 kPa, body surface cooling, using a water cooling mattress, to 32°C using an American Medical Systems Rk325 K Thermia EC 300 temperature control. All patients received analgesia with morphine by infusion (loading dose 100–200 µg/kg, then 20–40 µg/kg/hour) and sedation with midazolam (60–240 µg/kg/hour) except the first patients in the study who received other benzodiazepines, principally Diazemuls (Dumex). All patients were paralysed with atracurium 300–1200 µg/kg/hour, except the first patients in whom pancuronium was used. Intracranial pressure was monitored using a precoronal Richmond screw in 34 patients, subdural catheters in three, and not directly in two patients with extensive cranial fractures with suture diastasis. The pressure line was recorded on a Simonsen and Weel 8041 recorder. Arterial pressures were calculated by an S and W Pressure Module attached to an indwelling radial arterial cannula. The cerebral perfusion pressure was recorded by subtraction of the intracranial pressure from mean arterial pressure. Medical intervention was required if the intracranial pressure rose above 20 mm Hg, or the cerebral perfusion pressure fell below 50 mm

Table 1 Initial Glasgow coma scale (maximum=14)

	Frequency	*Range*	*Mean*
Normal	9	5–11	7·4
Minor handicap	13	4–11	6·1
Major handicap	8	3–6	4·3
Fatalities	9	3–6	4·1
All subjects	39	3–11	5·5

Hg. The patients were initially maintained on 50% normal maintenance requirements of fluids, and if prolonged monitoring was anticipated, total parenteral nutrition was started via a central venous catheter.

This process was reversed if the patient was thought to have suffered brain stem death, so that formal testing could be carried out, or after five days if the patient was in a stable condition. If, on warming the patient, intracranial pressure became unstable the process was recommenced for a further five days. If warming to 37°C was uneventful, normocapnia was allowed and then, if the patient was stable, the sedation was reversed, the intracranial pressure line removed, and the patient extubated and rehabilitation begun.

Outcome was assessed in four broad categories: neurological, cognitive, behavioural, and the presence of post-traumatic epilepsy. The surviving patients have been followed up for six months to five years, mean 2·5 years.

Results

The patients were divided into four groups according to outcome: intact survivors, those with minor or with major handicaps, and fatalities. Nine patients died and nine have survived intact. Twenty one patients have a degree of residual disability. Thirteen were assessed as having a minor handicap (table 2a). Two of these patients are currently undergoing rehabilitation and are anticipated to return to normality. Eight have been classified as suffering major disability with mental retardation and either spastic quadriplegia or hemiplegia (table 2b). Two of these were, however, neurologically abnormal before the injury.

The correlation between the outcomes and lowest mean blood pressure, highest intracranial pressure, lowest cerebral perfusion pressure, and lowest $PaCO_2$ are shown in table 3 and figs 1–3. There were significant differences

Table 2 Type of minor (a) or major (b) disability

(a) Minor disability (present in 33·3% of study group)	
Clumsy	2
Poor concentration/memory	3
Controlled post-traumatic epilepsy	1
Behavioural problems	2
Minor neurological signs	3
Problems walking[1]	2
Total	13
(b) Major disability (present in 20·5% of study group)	
Spastic quadriplegia, dysarthria, retarded	4†
Spastic hemiplegia, poor speech, retarded	4
Total	8

[1] Probably will be normal

†Two children neurologically abnormal *before* injury

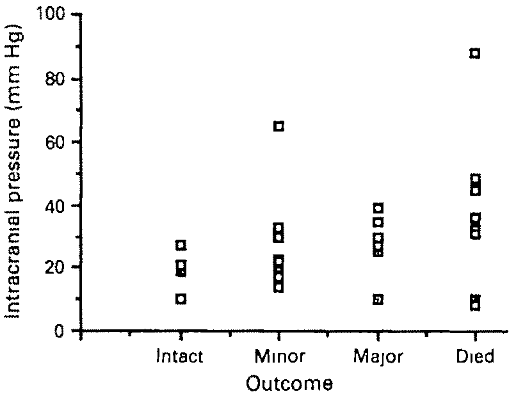

Figure 1 Intracranial pressure.

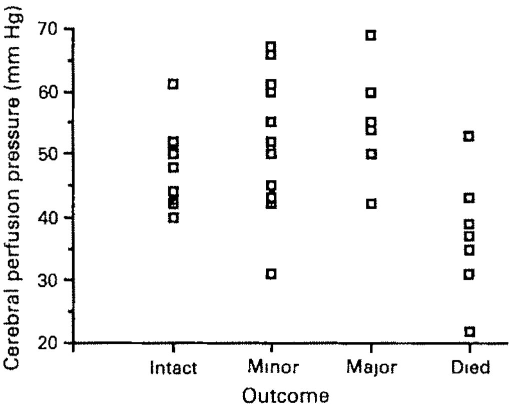

Figure 2 Cerebral perfusion pressure.

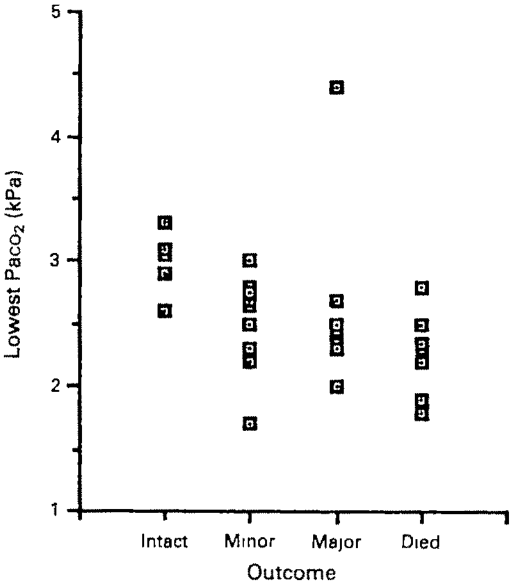

Figure 3 Lowest $PaCO_2$ in first 24 hours

Table 3 Relations of outcome to blood pressure, intracranial pressure, cerebral perfusion pressure, hypoxia (low PaO_2), hypocarbia (low $PaCO_2$). Results are range (mean)

Outcome	*Lowest mean blood pressure (mm Hg)*	*Highest mean intracranial pressure (mm Hg)*	*Lowest mean cerebral perfusion pressure (mm Hg)*	*Lowest mean PaO_2 (kPa)*	*Lowest $PaCO_2$ (kPa)*
Intact survivor	48–80 (60·4)	10–27 (18·8)	42–70 (50·6)	6·3–13·1 (9·1)	2·3–3·3 (2·8)
Minor handicap	30–92 (65·2)	14–65 (24·8)	31–67 (51·7)	6·2–10·6 (9·3)	2·2–3·1 (2·7)
Major handicap	47–100 (68·4)	10–39 (27·3)	42–69 (54·6)	6·4–10·0 (7·9)	2·1–4·4 (2·6)
Fatalities	40–75 (51·5)	8–88 (38·5)[1]	22–53 (34·5)[1]	5·8–18·0 (9·9)	1·8–2·8 (2·3)[1]

[1] p less than 0·05

in cerebral perfusion pressure between intact survivors and fatalities ($p<0.05$), and similarly for intracranial pressure and the lowest $PaCO_2$ recorded. No differences were observed in arterial oxygen tension (PaO_2), lowest mean blood pressure, and initial haemoglobin concentrations. Fifteen out of 30 patients who survived received total parenteral nutrition (TPN) for an average of 10 days. Two of the nine patients who died received TPN. The complications occurring during treatment are listed in table 4, with pneumonia most common in 25 of the 39 patients, including 21 of the 30 survivors (70%), as defined by radiographic changes, bacterial isolation, increased secretions, and increased oxygen requirements.

Analysis of 32 available computed tomograms at the end of the study by two radiologists performed blind to the clinical information was then correlated with outcomes (table 5). Particular attention was paid to signs of raised intracranial pressure (figs 4 and 5), the size of the basal cisterns and third ventricles (fig 6), to the presence of unilateral (fig 7) or bilateral contusions (fig 8), and to diffuse axonal injury (figs 9 and 10 A-D). In contrast figure 11 demonstrates no significant intracranial lesion despite a skull fracture following a serious head injury. When the basal cisterns and third

Table 4 Main complication

Complication	*No*
Pneumonia	25
Pneumothorax	4
Convulsions	9
Postextubation stridor	6
Diabetes insipidus	2
Morphine withdrawal	2
Infections	
Urine	2
Septic arthritis	1
Septicaemia	1
Eye keratitis	1

Table 5 Appearances on computed tomography (retrospective analysis)

	No of patients	*Good (normal+minor)*	*Poor (major)*	*Died*
(a) Clinical outcome associated with radiological indices of intracranial tension				
Normal third ventricle and cisterns	10	9	1	0
One or both compressed	12	4	4	4
One or both obliterated	10	4	3	3
(b) Clinical outcome associated with parenchymal lesions				
Unilateral*	7	5	1	1
Bilateral†	7	1	3	3
Diffuse axonal injury	9	4	2	3
Raised intracranial pressure‡	4	2	2	0
Normal	5	5	0	0

*Unilateral equals contusions in one cerebral hemisphere or an ipsilateral cerebellar hemisphere
†Bilateral equals contusions in both cerebral or cerebellar hemispheres
‡Raised intracranial pressure without parenchymal lesions

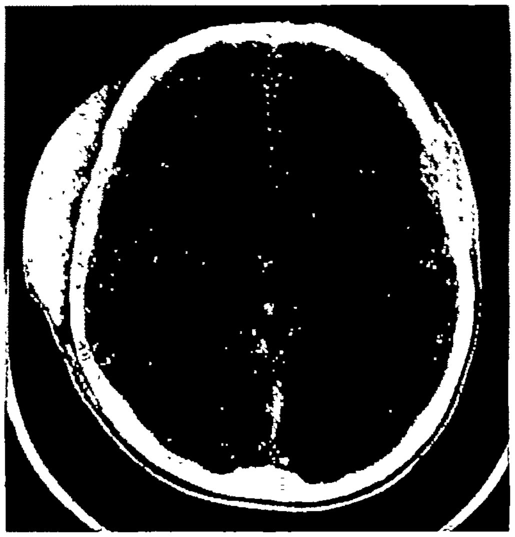

Figure 5 Computed tomogram showing later raised intracranial pressure, obliteration of the third ventricle, and slit-like compressed lateral ventricles. A large subgaleal haematoma is present in the right frontotemporal region.

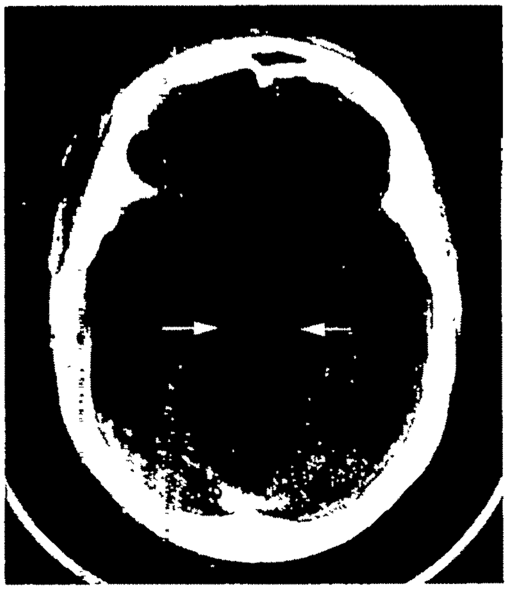

Figure 4 Computed tomogram showing early raised intracranial pressure and obliteration of the ambient cisterns.

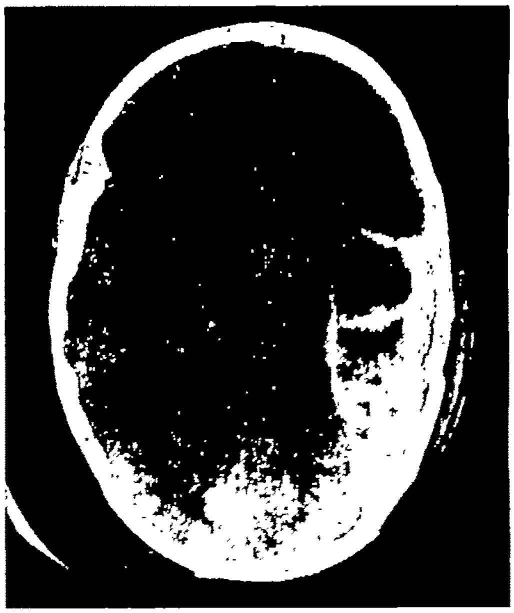

Figure 6 Computed tomogram showing a large acute left frontotemporo-occipital extradural haematoma with marked mass effect and obliteration of the third ventricle Note internal loculations and pseudomembranes.

ventricle were normal 90% of patients had a good outcome (normal or minor disability) whereas if compressed or obliterated 32% had major handicap and 32% died. When unilateral contusions occurred 71% had a good outcome, but with bilateral contusions only 14% had a good outcome. If diffuse axonal injury was noted 56% had a poor outcome. In the three patients with diffuse axonal injury and contusions all had a poor outcome.

Discussion

The results of this study compare favourably with other reported series, with 56% making a good recovery with normal outcome or minor disability only compared with 36% reported by Becker *et al*[2] and 45% in the series of Marshall *et al*[1] (table 6). As in other series[8] the majority of our patients had been struck by motor vehicles.

The use of surface cooling enabled the avoidance of barbiturate coma, and this meant that assessment of brain stem death could be made earlier. When confirmed this would enable earlier donor organ retrieval, and may improve the likelihood of successful donation from such unstable patients.

The observation that intracranial pressure was highest in non-survivors was not surprising, nor was the lower cerebral perfusion pressures in this group. The approximate cut off of 40 mm Hg for cerebral perfusion pressure delineating survivors and non-survivors was in accordance with previous studies.[9]

Analysis has demonstrated a poorer survival with lower $Paco_2$ in the first 24 hours. Similar findings have been reported,[10] suggesting that excessive hyperventilation early on after head injury may reduce cerebral blood supply below a level necessary to nurture the basal metabolic level of an already insulted brain. Although the numbers studied here were small, further analysis of possibly harmful hyperventilation in such critically injured patients is required. We would suggest frequent blood gas analysis, the use of end tidal carbon dioxide measurements and caution with over enthusiastic hand ventilation

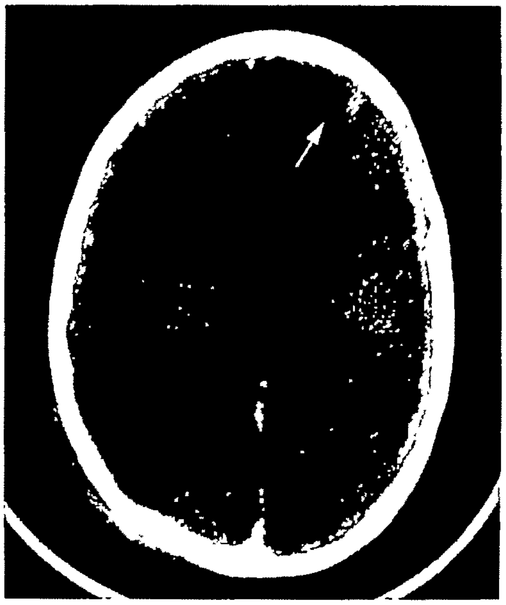

Figure 7 Computed tomogram showing a unilateral left frontal haemorrhagic contusion (arrow).

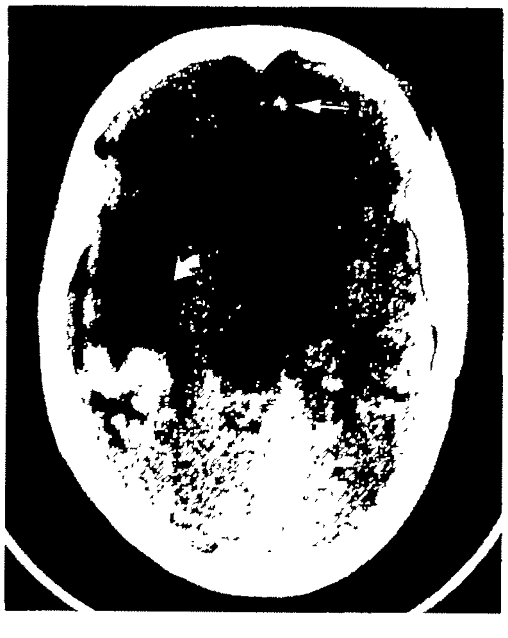

Figure 8 Computed tomogram showing a small left frontal haemorrhagic contusion (straight arrow) and a large right temporo-occipital haemorrhagic contusion. The temporal horn of the right lateral ventricle is distorted by the local mass effect (curved arrow)

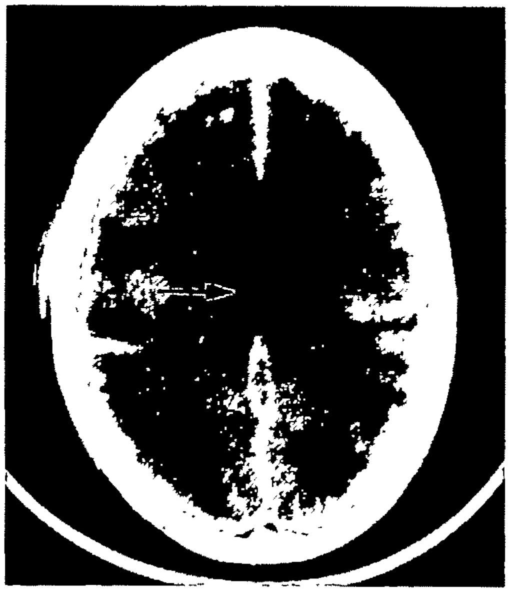

Figure 9 Computed tomogram showing diffuse axonal injury and widespread cortical and subcortical haemorrhagic contusions in both cerebral hemispheres Note also a subtle typical haemorrhagic contusion in the region of the body of the corpus callosum (arrow).

Table 6 Outcome comparison with other studies (%)

	Becker et al[2] *(n=160)*	*Marshall et al*[1] *(n=100)*	*Elias-Jones et al (n=39)*
Good recovery	36	45	56
Moderate disability	24	15	21
Severe disability	10	12	
Died	30	28	23

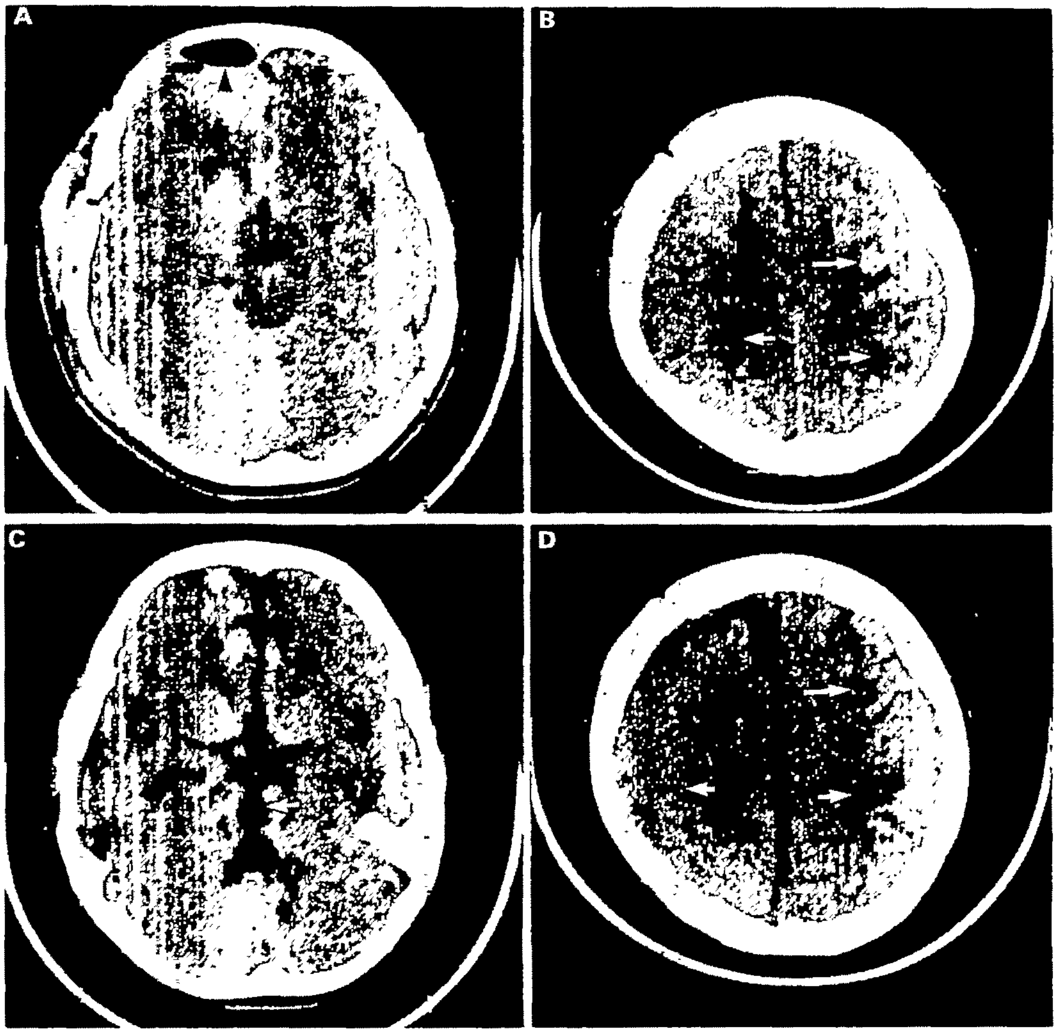

Figure 10 (A) Computed tomogram showing an example of diffuse axonal injury; a compound right temporal bone fracture with intracranial air overlying the right frontal pole and in the right ambient cistern is shown by arrowheads. Note early subtle brain stem contusion (small arrow). (B) Same patient showing gyral contusion in the left posterior frontal region (arrow). Note a thin right convexity subdural haematoma (arrowhead) and small subcortical white matter linear lesions (small arrows). (C) Same patient four weeks later showing that encephalomalacic lesion has developed centrally within brain stem (arrow). Note development of generalised atrophy in both the supratentorial and infratentorial compartments with dilatation of temporal horns, basal cisterns, and fourth ventricle. (D) Part of the same scan as (C) showing a focal area of encephalomalacia has developed at the site of the left posterior frontal gyral lesion (arrow). Further subcortical white matter lesions are once again seen possibly representing gliding lacerations (small arrows)

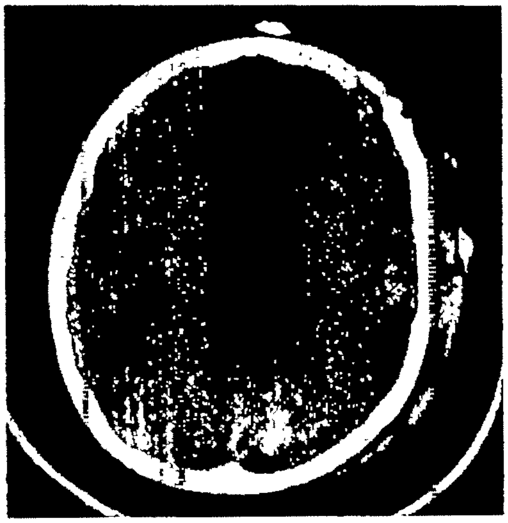

Figure 11 Computed tomogram showing a normal brain scan after serious head injury consequent to a heavy blow from a blunt instrument causing a comminuted left frontal fracture. There is no significant intracranial lesion present

of such patients, aiming for a $Paco_2$ in the band of 3·5–4·0 kPa.

Analysis of the computed tomogram appearances has borne out other studies that obliteration of basal cisterns and the third ventricle is a worrying sign.[11] [12] Combinations of contusions and diffuse axonal injury predict poor outcome in the few patients in this study.

The initial Glasgow coma scores, while showing a trend to be lower in patients with poor outcomes, show considerable overlap between patient groups such that they cannot be relied upon to act as a basis for withholding full intensive care treatment.

The incidence of pneumonia noted in this study was high; however this is a common occurrence in ventilated patients some of whom may also have aspirated at the time of injury. Although it is possible that surface cooling encourages pneumonic attack, the administration of antibiotics with physiotherapy dealt effectively with this complication, and did not prejudice survival. Many of the patients were also receiving cimetidine which is also known to encourage bacterial pneumonia,[13] and has led us to turn to alternative protective agents.

CONCLUSION

This study has demonstrated that a policy of surface cooling is effective and obviates the need for barbiturates and all the concomitant problems associated with the latter.

Analysis of the initial Glasgow coma scores has shown considerable overlap; however a good outcome is expected if the score is 7 or more, whereas a score of 3 predicts death or severe permanent disability. A poor outcome is also associated with a low $Pa\mathrm{CO}_2$ ($\lesssim 3{\cdot}0$ kPa) and a low cerebral perfusion pressure (<40 mm Hg). Consequently, maintenance of an adequate cerebral perfusion pressure over 50 mm Hg should be a primary aim of the treatment protocol.

Radiological appearances that carry a poor prognosis are obliterations of the basal cisterns and third ventricle, bilateral hemispheric contusions and/or diffuse axonal injury.

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Long term effects of periconceptional multivitamin supplements for prevention of neural tube defects: a seven to 10 year follow up

Monica Holmes-Siedle, Jennifer Dennis, R H Lindenbaum, Annona Galliard

Abstract

Periconceptional supplementation with Pregnavite Forte F was offered to women who presented consecutively to the Oxford genetic counselling service in the early 1980s who had previously had one or more pregnancies complicated by a neural tube defect. The first 100 children born alive to these women are the subject of this study. Birth weight, gestation, and congenital abnormalities were recorded. At age 2–5 years all 96 children remaining in the United Kingdom were assessed clinically and developmentally and behavioural information was obtained by questionnaire. At age 7–10 years, follow up of 91 children by telephone and postal questionnaire yielded further information about growth, general health, vision, hearing, and educational and behavioural status. Entry criteria excluded single mothers but the social class distribution of the sample was otherwise representative of the Oxfordshire population. There were no recurrences of neural tube defects. One child had radiological evidence of spina bifida occulta affecting only the fifth lumbar vertebra. One had an autosomal recessive disorder. Eight had random minor congenital anomalies. Birth weight for gestational age was significantly greater than for the local population and at age 7–10 years the girls were considerably taller than expected. Health, auditory, visual, and developmental status were no different from the general population. None of the children had special educational needs. None showed a major behaviour disorder but worries, fussiness, and fearfulness were highly significantly over represented.

(*Arch Dis Child* 1992;67:1436–41)

Periconceptional supplementation with Pregnavite Forte F (Bencard) as a primary prevention of neural tube defects has been carried out in various centres in the United Kingdom for more than a decade.[1–3] The publication of the results of the Medical Research Council trial showed similarly successful results for high doses of folic acid alone.[4] This will give added impetus to periconceptional treatment.

The administration of any drug to women during the critical period of organogenesis in the embryo is best avoided. In the original studies care was taken to monitor any birth defects present. This confirmed that no overt harm had been caused to the children by the multivitamin treatment.[5 6] The possibility must be examined, however, that the vitamin treatment may have more subtle or indirect effects only seen later in life. This paper describes a long term study which addresses this question. We present medical, developmental, and behavioural data up to the age of 10 years for an unselected group of 100 children whose mothers received supplementation with multivitamins and folic acid in the periconceptional period.

Subjects and methods

SUBJECTS

The subjects were women who had previously had one or more pregnancies complicated by a neural tube defect and presented consecutively to the Oxford genetic counselling service. They were with the same partners as for the previous pregnancy but were not yet pregnant again. These women were offered periconceptional supplementation according to the Smithell's protocol.[7] The supplement used was Pregnavite Forte F, a multivitamin preparation which includes folic acid (0·36 mg daily) and minerals. Those who accepted and took this for a minimum of 28 days before conception and continued at least until the second missed menstrual period were regarded as fully supplemented. The complete lack of recurrence of neural tube defects in the offspring of these Oxford women has been reported in the multicentre study of Seller *et al.*[6] The children in the present study were the first 100 children born alive to this group of women. This unselected group represents the offspring of 93 women who delivered between April 1981 and June 1984. Six of these women had had two previous pregnancies complicated by neural tube defects and 87 one such previous pregnancy. Seven had two pregnancies during the study period and there was one twin pair. The mean length of preconceptional supplementation was 128 days; the maximum was 437 days. After conception the mean supplementation period was 107 days and the maximum 252 days.

METHODS

Birth information

Information about birth weight and gestation was obtained from contemporaneous records at the time of delivery. Information about congenital abnormalities was obtained from contemporaneous records supplemented by information from the women at the time of first follow up.

First follow up (age 2–5 years)

Children were seen in their own homes by the

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principal investigator (MH-S). They were examined clinically and information about their general health and specific problems was obtained in standard format. Head circumference and height were measured. If a child had recently passed a health visitor's hearing test no further hearing check was made but if not, children were tested using a Manchester rattle and the seven toy speech discrimination test. Vision was checked by the Stycar vision test[8]; gross and fine motor, language, and social skills were assessed using the Denver developmental screening test (DDST)[9] and the Richman behaviour screening questionnaire (BSQ)[10] was completed by the parents.

Second follow up (age 7–10 years)

The children were not seen personally. All the mothers were interviewed by telephone by MH-S following a standard format. Information was sought about general health together with their agreement to complete a postal questionnaire. This produced information on height, weight, vision, hearing, and educational status. The parents were asked to comment on their child's development in relation to other children of the same age and to complete the Rutter behavioural scale (A2, for parents).[11]

Results

Maternal age at delivery ranged from 22 to 39 years (mean 29·2 years). Social class distribution, as determined by paternal occupation, differed from 1981 census figures for Oxfordshire[12] in that only 3% were ascribed to the category 'other' in contrast with 24% in the county. This is because a criterion for inclusion in this study was that the women should be with the same partner as when their previous child with neural tube defects had been conceived. This made it unlikely that single mothers would be included. When this difference was allowed for the distribution within social classes I–V did not differ from the county population.

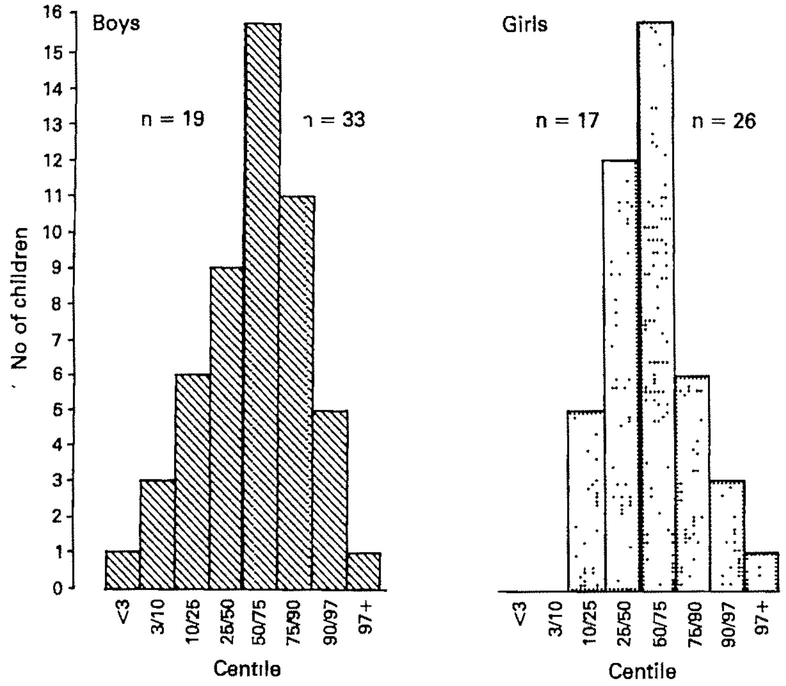

Figure 1 Supplemented group. Distribution of birth weight for gestational age for singleton births according to Oxford standards.[13]

FIRST FOLLOW UP

Follow up was achieved for all 96 children still resident in the United Kingdom. There were 52 boys and 44 girls. Age ranged from 22 months to 5 years (mean 3 years 6 months). Most were 2, 3, or 4 years old.

Birth information

Information about birth weight and gestation was reliably available for 97 of the original sample of 100, including one twin pair. Ninety of the singleton pregnancies (95%) had continued beyond 38 weeks. Four babies (4%) had been born at 37 weeks and one (1%) at 36 weeks. The distribution of birth weight for gestational age for singleton births was slightly skewed to the right (fig 1) compared with Oxford standard birth charts.[13] The excess of birth weights above the 50th centile was significant at the 1% level.

Congenital abnormalities

After reporting backache at the age of 5 years, one child showed radiological evidence of a small spina bifida occulta affecting only the fifth lumbar vertebra. She was one of a same sexed twin pair whose mother had previously given birth to one anencephalic and one normal girl. There were nine other children with abnormalities. One had an autosomal recessive disorder (oculocutaneous albinism). The other abnormalities were one child each with pyloric stenosis, terminal hypospadias, thyroglossal cyst, left congenital corectopia (displaced pupil), positional talipes, and three boys with unilateral cryptorchidism.

Clinical findings

Inspection of the spine showed a skin covered sacral dimple in three children, one of whom had a father who was said to show a similar feature. The child with congenital corectopia had astigmatism, one child had a right convergent squint, and two were myopic. One child had brief absences. Three children had mild hearing loss due in one child to mumps meningitis and in the others to glue ear.

Growth

Data for height and head circumference (OFC) were analysed separately by sex and expressed as centiles for age according to Tanner-Whitehouse standards.[14] The distribution of height for both sexes was slightly but not significantly skewed to the right. Head circumference showed a similar trend. As the OFC distribution among the general Oxford population was known to differ from Tanner-Whitehouse standards centiles were reassigned according to the data of Ounsted *et al*[15] and a close match was achieved. This suggests that the height discrepancy may also have arisen because the Tanner-Whitehouse norms are not relevant to our local population.

Development

No child either 'failed' or was ascribed 'questionable' developmental status according to the set criteria for scoring the DDST. Four children (4%) showed delay in the language sector of the test. This sector of the screening test shows poor sensitivity and identifies only 53% of children who have expressive language delay on formal speech and language evaluation.[16] Richman *et al*, on formal evaluation, identified language delay in 20 of 105 (19%) 3 year olds in an outer London borough[17] and Silva identified expressive language delay in 13% of unselected Dunedin 5 year olds.[18] Thus language delay in the study group, even allowing for the poor specificity of the test used, is unlikely to have been greater than in the general population.

Behaviour

Only one girl and one boy achieved scores of 11 or more on the BSQ, which is the cut off point suggesting behavioural disturbance. This represents only 2% of the study group (two of 96). Stevenson and Richman found 14% (101 of 705) of 3 year olds in an outer London borough scoring above this cut off,[19] and in the original standardisation test sample five of 57 'controls' (9%) were in this range. It thus seems that overall our study sample showed a low level of behavioural disturbance compared with the general population. Item by item analysis showed fewer high scorers on all items except 'worries' where 4% scored 2 as opposed to 2·3% of the Stevenson sample. This difference does not reach statistical significance but is of interest in relation to findings in the second follow up.

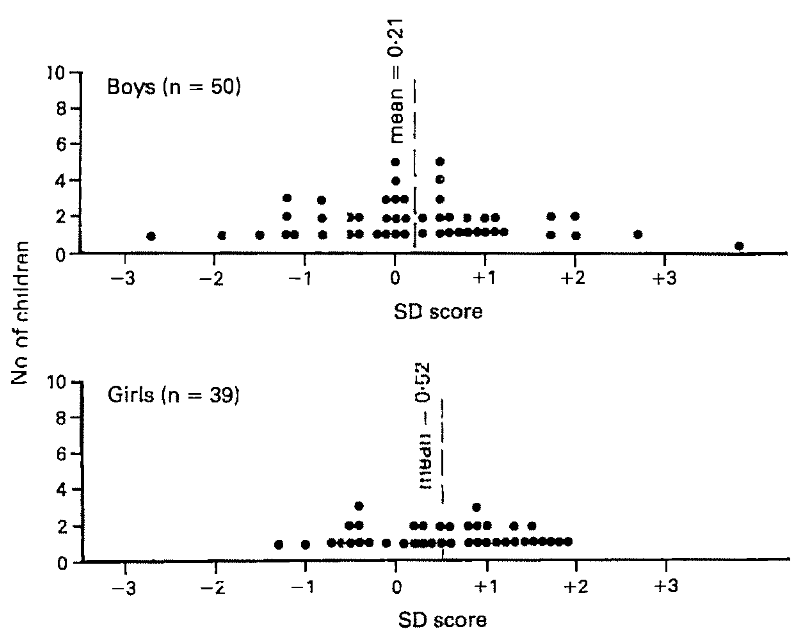

Figure 2 Supplemented group. Height at age 7–10 years. Distribution of SD scores according to Tanner and Whitehouse.[15]

SECOND FOLLOW UP

One further child had left the United Kingdom since the first follow up, two families were untraceable, and two families, though completing the telephone interview, did not return the questionnaires. This left 91 children in the second phase of the study, 51 boys and 40 girls. Ages ranged from 7·1 to 10·2 years (mean 8·8 years).

General medical problems

Respiratory problems, either current or previous, were reported for 13 children (14%). These children were described as having 'asthma' or as being 'chesty'. Seventeen (19%) had had accidents, 13 (14%) having sustained fractures. Eleven (12%) were reported to have congenital/genetic disorders; 10 of these had been identified at the first follow up and the additional case was a previously unreported hydrocele. Sixteen (19%) children had had ear, nose, and throat problems, mainly glue ear. Eight children wore spectacles and a further five had ocular problems, giving a total of 14% with visual problems. Two (2%) had had meningitis (one mumps, one meningococcal). There were 13 other miscellaneous problems. No problem group was over represented when compared with the general population of 7–10 year olds. Eighty four per cent were right handed, 13% left handed, and 3% ambidextrous.

Growth

Height measurements taken by mothers were analysed separately by sex and expressed as SD scores according to Tanner-Whitehouse standards (fig 2). The means for both sexes (boys +0·21 SD; girls +0·52 SD) were greater than the Tanner-Whitehouse norms, that for girls being significantly more so ($p<0·02$). These findings show that the heights of the children in the study at 7–10 years of age show the same upward shift compared with Tanner-Whitehouse norms as is found in all children in Oxfordshire at ages 3 and 4·5 years (D Dunger and J A Macfarlane, personal communication).

Behaviour

Children who score 13 or more on the Rutter A2 scale are likely, on clinical evaluation, to be diagnosed as having psychiatric disorders. In this study five of 51 boys (10%) and one of 40 girls (3%) scored at or above this cutoff point. Taking both sexes together six scored above the cutoff against an expected figure of 5·4 derived from Isle of Wight control subjects aged 9–12 years.[11] Thus the level of psychiatric disorders among the study group appears to be similar to that found in the general population.

The 18 items scored on the Rutter scale can be grouped into four behavioural domains reflecting motor activity, relationships, antisocial behaviour, and neurotic traits. The scale has been adapted for 5 year olds by excluding two of the 18 items which are predominantly developmentally determined and Yule has obtained general population data for 396 Isle

Rutter behavioural scale item by item comparison with general population figures

	Siblings of those with neural tube defect (vitamin supplement sample) (n=91)	*Isle of Wight general population§ (n=396)*	*Isle of Wight general population*[11] *(n=2189)*
Boys	51	192	—
Girls	40	204	—
Age (years)	7–10	5	9–12
	No (%)	*No (%)*	%
Motor items			
Restlessness	23 (25)†††	206 (52)†††	31
Fidgety/squirmy	16 (18)	93 (23)	12
Twitches/tics	2 (2)	11 (3)	4
Unable to settle	10 (11)††	88 (22)†	22*
Relationships			
Irritability	30 (33)	138 (35)	30
Not much liked	4 (4)	7 (2)	5
Solitary	16 (18)	104 (26)	23
Antisocial			
Destructive	4 (4)	50 (12)	4
Disobedient	35 (39)†	195 (49)	26*
Lies	26 (29)††††	71 (18)†	11***
Bullies	3 (3)	25 (6)	5
Fights	16 (18)†	68 (17)	10*
Neurotic			
Worried	48 (53)††††	108 (27)†††	39*
Miserable	19 (21)*†	76 (19)	11**
Fearful	39 (43)†††	81 (20)	27***
Fussy	25 (27·4)†††	69 (17)†	16**

*p<0·05; **p<0·01; ***p<0·005, comparison with 9–12 year old general population group
†p<0·05, ††p<0·01, †††p<0·005, comparison with 5 year old general population group.
χ^2 corrected for continuity.
§Personal communication, W Yule.

of Wight 5 year olds using this adaptation (W Yule, personal communication). Item by item analysis (see table) was carried out comparing the study group with the two Isle of Wight samples. This shows that compared with these general groups those items which reflect motor restlessness and attention deficit were scored less often for the study group while those reflecting neurotic traits (worries, misery, fearfulness, and fussiness) were notably, and often significantly, over represented. With respect to antisocial items, a tendency to disobedience and fighting appeared to be developmentally graded but significantly more of the study group children told lies than in either the 5 or 9–12 year old population groups.

Schooling

All children were in mainstream schools. None had attended special needs provision either at nursery or school age. One 9 year old was receiving help from a speech therapist and three other children had had speech therapy in their preschool years. Eight of the children (8%) were receiving extra help in school with reading, writing, or other learning skills. All these children were above the age of 8·5 years (mean age of sample 8·8 years).

Discussion

In our group of 100 children at relatively high risk of a neural tube defect because of a previously affected sibling, three or four lesions of the neural tube would have been expected. No open lesions were present but in this detailed examination one child with spina bifida occulta was identified; this affected the fifth lumbar vertebra only. Fawcitt's review suggests that the incidence of spina bifida occulta may be as high as 94% in the 0–5 year old group,[20] with isolated L5 defects occurring in 15% of this group. If radiographed after a few years, it is likely that these children would be considered to be normal. Thus we believe that the spina bifida occulta found in one child in this study should not be regarded as a recurrence of a neural tube defect. Similarly the finding of three children with a skin covered sacral dimple is within the expected range as stated by Méhes.[21] There was no increase above expected numbers for other congenital malformations. This adds further support to evidence that Pregnavite Forte F is not teratogenic.

A higher proportion of pregnancies progressed to term than is usual, the birth weights for gestational age of the children were greater than expected for the local population, and there is some suggestion that growth has been enhanced among the girls. This latter finding cannot be confirmed until contemporary growth standards for the United Kingdom population become available.[22]

The children have all had good health and there is no evidence that major learning difficulties or sensory impairment are over represented. The possibility that subtle cognitive deficits could nevertheless be present could only be tested by individual neuropsychological assessment.

The behavioural findings are of interest in that worries, fearfulness, and fussiness are notably over represented among the 7–10 year olds and a trend towards being overworried was already emerging in the same group at an age of 2–5 years. The simple explanation of this is that these neurotic traits have arisen secondarily to maternal anxiety about the child. All the women had had a previous pregnancy with a neural tube defect. For many this had resulted in the birth of a liveborn child and all that entailed in terms of handicap, suffering, and death. For most of the women the children in this study were the first to be born after the affected child. It would not be surprising if maternal anxiety about these children extended far beyond the early months of pregnancy and if their previously distressing experiences of childrearing determined a style of parenting likely to produce anxiety in the child. There was indeed anecdotal evidence from the women that this was so. For instance, one mother of a 9 year old child recounted that she still remained outside the school gates for 10 minutes after the children had gone in, feeling unable to leave in case her child needed her.

This interpretation of the findings must, however, be set alongside the fact that worries, fearfulness, and fussiness can be organically determined. The most compelling information derives from two studies. Udwin and coworkers have evaluated the psychiatric aspects of children and adults with Williams' syndrome (idiopathic infantile hypercalcaemia).[23 24] The Rutter parent scale was used and as in the study reported here the findings were compared with the Isle of Wight control data. A second comparison group was a group of children with mental handicap from causes other than idiopathic infantile hypercalcaemia. A distinct behavioural phenotype including a high incidence of worries, fearfulness, and fussiness was found for the children with idiopathic infantile hypercalcaemia and these features were enhanced and often disabling in adult life. The conclusion was that these features were likely to be biologically determined. The second study which supports this idea is that of Shaffer *et al* who examined the relation between neurological 'soft signs' and behaviour in a subsample of 7 year old children who had been enrolled in the US collaborative perinatal project in 1962 and 1963.[25] Those with 'soft' signs scored significantly higher on the dependency/withdrawal scale (which included ratings for fearfulness, self confidence, and need for attention/help), but not on the hyperactivity or aggression scales. This pattern of psychiatric functioning is similar to some of the siblings of children with neural tube defects in this study.

In the context of this study it is possible that these features represent a behavioural phenotype associated with the genetic determinants of neural tube defects. Vitamin supplementation could prevent expression of the major physical manifestation but not all other genetic effects. The possibility also has to be considered that the behavioural attributes could be actually determined by periconceptional vitamin supplementation. The relative importance of all three possible determinants (parenting style, genetic influences, and periconceptional vitamin supplementation) could be tested by a relatively simple multicentre behavioural study of children including those born before and after an index child with a neural tube defect and those born after an index child with a neural tube defect who have or have not had periconceptional supplementation with Pregnavite Forte F. Databases exist in sufficient centres to make this possible and the findings would be of great importance for families at risk of neural tube defects.

It must be noted here that it is not possible to speculate on the applicability of our results to the children reported in the recent Medical Research Council randomised multicentre study.[4] In that study mothers received folic acid alone (4 mg/day) during the periconceptional period. Pregnavite Forte F provides only 0·36 mg folic acid daily together with a cocktail of vitamins and minerals.

CONCLUSIONS

Periconceptional vitamin supplementation had a protective effect on 100 children assessed in that there was no recurrence of neural tube defects. No harmful effect was detected. A possible beneficial effect was noted on growth. Over representation of worries and anxiety among the children at age 7–10 years merits further inquiry.

We are grateful to Professor Martin Bobrow who suggested the original study and to our colleagues for their advice and encouragement, in particular Dr Mary Seller, Professor RW Smithells, and Professor John Edwards. We also thank family members of MH-S and JD for help in collating the data Secretarial assistance was provided by the department of medical genetics, in particular Anne Naylor and Peggy Ducker We are grateful to the patient who gave us a financial contribution, to the referring doctors, and for the supply of vitamins from the John Radcliffe Hospital pharmacist and Bencard Finally our warm thanks go to the study families for their patient cooperation over the past few years.

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Not by vitamin A alone

A good deal of excitement has been generated by trials showing considerable reductions in mortality in children in Asia given supplements of vitamin A (see Archivist 1992, p288). Now a trial done in northern Sudan points to possible limitations of this approach (M Guillermo Herrera and colleagues, *Lancet* 1992;**340:** 267–71).

In a double blind placebo controlled trial 28 753 children aged between 9 and 72 months were given either 200 000 IU vitamin A plus 40 IU vitamin E or 40 IU vitamin E alone every six months for three doses. Those with clinical evidence of xerophthalmia were treated with vitamin A and excluded from the trial. No effect on mortality was demonstrated. Of 14 455 children given vitamin A 123 died and in the placebo group there were 14 298 children and 117 deaths. No subgroup was identifiable in whom vitamin A significantly reduced mortality. Signs of xerophthalmia were reduced but not abolished in the treated group.

There are a lot of unanswered questions. Other studies in which the vitamin has been given more frequently (200 000 IU every four months) or in a lower dose much more frequently (8333 IU weekly) have shown reductions in mortality of between 30 and 54%. It may simply be, therefore, that a dose of 200 000 IU every six months is not enough. There is evidence that supplementation is more effective where existing rates of mortality are higher. It is possible too, that vitamin A supplementation is more effective in areas where natural vitamin A intakes are lowest but the evidence from the trials done so far would not suggest that. Other factors which may alter the effect of giving vitamin A include diet, intestinal parasites, and prevalent bacterial or other pathogens. In this study a low baseline dietary intake of vitamin A was associated with increased mortality suggesting that dietary fortification might be more effective than giving large doses infrequently.

The study is a reminder, if one is needed, that vitamin A supplementation, important as it may be, cannot be the whole answer. Reducing poverty, improving nutrition, and reducing the burden of microbiological assault must remain the goals.

ARCHIVIST

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A randomised trial of low dose folic acid to prevent neural tube defects

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Abstract

A randomised trial was initiated in Ireland in 1981 to determine if periconceptional supplementation with either folic acid alone or a multivitamin preparation alone could reduce the recurrence risk of neural tube defects (NTDs) in women with a previously affected pregnancy from 5·0% to 1·0% or less. The trial was concluded before the initial target number of study subjects was reached and without a clear treatment effect being observed. A total of 354 women were randomised to receive one of three treatments: folic acid, multivitamins without folic acid, and folic acid plus multivitamins. At the end of the trial 257 women had had a first trial pregnancy outcome (261 infants/fetuses) where the presence or absence of NTDs was ascertainable. There was one NTD recurrence in the 89 infants/fetuses of women in the multivitamin group and no recurrence in the 172 infants/fetuses of women in the folic acid groups, a non-significant difference. Otherwise eligible women who were pregnant when first contacted constituted a non-randomised control group; there were three recurrences among the 103 infants in this group. The difference in the recurrence rate between the folic acid groups and the non-randomised controls was statistically significant but we have reservations about the validity of this comparison. Although our findings do not provide clear evidence of a protective effect of folic acid supplementation they are consistent with those of the Medical Research Council (MRC) trial which demonstrated the efficacy of folic acid in preventing recurrence of NTDs and they raise the possibility that folic acid may be protective at a much lower dosage than that used in the MRC trial.

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In 1980 Smithells *et al* reported the results of a non-randomised study showing a reduction in the prevalence rate at birth of neural tube defects (NTDs) from 5% in unsupplemented mothers to 0·6% in mothers given periconceptional vitamin supplementation (Pregnavite Forte F, Bencard).[1] Because of the high frequency of these births defects in Ireland[2] and the problems in drawing conclusions[3] from the studies by Smithells *et al*[1 4] and Laurence *et al*,[5] a randomised double blind trial was launched in Dublin in 1981 to determine if periconceptional supplementation with either folic acid alone or a multivitamin preparation alone could reduce the recurrence risk of NTDs in women with a previously affected offspring. Subsequently a randomised trial examining this issue was initiated in 1983 by the British Medical Research Council (MRC) and the results have recently been published.[6]

Methods

The study was conducted in 12 Irish hospitals, four of which were in Dublin, with the Health Research Board as the coordinating centre. The participating clinicians and hospitals are given at the end of the paper.

AIM AND SAMPLE SIZE

The aim of the trial was to determine if periconceptional supplementation with either folic acid alone or a multivitamin preparation alone would reduce the recurrence risk of NTDs in women with a previously affected offspring from 5% to 1% or less. This was similar to the reduction achieved by Smithells *et al.*[1 4]

Various experimental designs were considered including a randomised four arm factorial study with a placebo group receiving no active treatment. Though the final choice of three groups had certain disadvantages, we felt that the possibility of being assigned to a placebo group could, in the light of the publicity at the time (1981) about Pregnavite Forte F and vitamins generally, be a cause of undue anxiety to participants and could adversely affect recruitment. Thus the main analysis of our study was based on two comparisons. The proportion of births of NTDs occurring to women taking multivitamins (two thirds of the sample) was compared with the proportion occurring to women not taking multivitamin tablets (one third of the sample) and the second comparison was similarly between women receiving folic acid and those not receiving folic acid.

On the assumption that either folic acid alone or multivitamins alone reduced the recurrence rate of NTDs from the population level at that time[7] of 5·0% to 1·0%, a total sample of 462 pregnancy outcomes (154 in each group) was required for our trial to have an 80% chance of detecting this at a 5% level of statistical significance.

Ethical approval for the trial was obtained from each participating hospital and recruitment commenced in December 1981. We estimated that our target number of informative (presence or absence of NTD ascertainable) pregnancies might be reached by 1989 but unanticipated declines of 65% in the prevalence at birth of NTDs and 20% in the number of births in the Dublin maternity hospitals over the study period greatly reduced the number of affected births and when the rate of recruitment fell to an average of 1·3 women per month in late 1987 it was decided to end the trial. Randomisation ceased in January 1988 and 30 April 1990 was set as the closing date for the entry of pregnancy outcomes to data analysis.

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*Members of the Irish Vitamin Study Group are given at the end of the paper

ENTRY AND EXCLUSION CRTIERIA

Women who had had a baby with a NTD and who were not pregnant when contacted by the study team but were planning a further pregnancy were eligible for inclusion. A NTD was defined as anencephalus, iniencephalus, encephalocoele, and spina bifida aperta. Women with conditions likely to result in impaired absorption from the gastrointestinal tract were excluded.

RECRUITMENT AND RANDOMISATION

Potential study subjects were identified by means of registers of cases of NTDs in participating hospitals. Eligible women were invited to discuss the trial and were given relevant information. Women who entered the trial gave verbal consent and were randomly allocated to one of three treatment groups: folic acid only (group F), multivitamins excluding folic acid (group M), and folic acid plus multivitamins (group FM). Random allocation was achieved by using consecutively numbered, opaque, sealed envelopes. Block randomisation was employed, 12 subjects per block, stratified by hospital.

TRIAL MEDICATION

The study was designed as a double blind trial. Beecham Pharmaceuticals (UK) initially provided similarly presented white multivitamin tablets without folic acid (Pregnavite Forte) and with folic acid (Pregnavite Forte F—as used by Smithells *et al*[1 4]). Glaxo (Ireland) Ltd manufactured a matched folic acid tablet. Although Beecham Pharmaceuticals (UK) initially agreed to supply the tablets for the full duration of the study their support was withdrawn one year later when 55 mothers had been randomised. Thereafter the commercially available Pregnavite Forte F (purple colour) was used and Antigen Pharmaceuticals produced a white multivitamin tablet without folic acid. It is felt that this partial loss of blinding did not materially affect the study outcome.

Trial participants were instructed to take one tablet three times daily for at least two months before conception and until the date of the third missed period. Compliance was based on tablet counts and blood tests but these results are not reported here. Tablets for women in the folic acid groups provided a daily dose of 0·36 mg of folic acid (0·12 mg/tablet). Tablets in the multivitamin groups provided daily doses of vitamin A 4000 IU, calciferol 400 IU, thiamine hydrochloride 1·5 mg, riboflavine 1·5 mg, pyridoxine hydrochloride 1 mg, nicotinamide 15 mg, ascorbic acid 40 mg, calcium phosphate 480 mg, and ferrous sulphate 252 mg.

Throughout the trial Hoffman La Roche in Switzerland and Glaxo in Ireland carried out regular assessments of the stability of the multivitamin and folic acid tablets, respectively.

STATISTICAL ANALYSIS

Statistical analysis was based on 95% confidence intervals (CI) and two sided hypothesis tests with a 5% level of significance. For continuous variables the Student's *t* distribution was employed for significance tests. For the analysis of 2×2 tables comparing rates in two groups, an uncorrected χ^2 test was employed in all situations. Use of the uncorrected χ^2 gave rise to some statistically significant effects in situations where the usually accepted method, Fisher's exact test, failed to do so. There is now, however, an increasing body of literature which states that neither Fisher's exact test nor Yates's corrected χ^2 are appropriate tests for tables arising from particular types of study design including clinical trials.[8] It is now suggested that the uncorrected χ^2 should be used for all such 2×2 tables including those with small numbers where expected frequencies fall below five.[9] Group comparisons in 2×2 tables were based on the difference between the component rates or proportions. The CI were test based[10] using the uncorrected χ^2 test. Social class, based on husband's occupation, was coded using the Irish Central Statistics Office's social class code.[11]

Results

During December 1981-January 1988, 354 eligible women were randomised as follows: 115 to the folic acid group (F), 119 to the multivitamin (no folic acid) group (M), and 120 to the folic acid plus multivitamin group (FM). Altogether 81·4% of the women were randomised in the four Dublin hospitals.

At the time of contact by the study office 116 otherwise eligible women were pregnant and thus could not be randomised. Ten of these women entered the trial after this pregnancy and they are included in the analysis as trial participants only. The remaining 106 are included as a non-randomised control group.

Selected baseline data and pregnancy status at the end of the trial are presented for the three randomised groups and the non-randomised control group in table 1. When the trial ended in April 1990, 263 women who remained in the trial had completed a pregnancy, 16 women were not pregnant, and 75 had withdrawn from the study (table 1). After withdrawal, 18 of the 75 women completed a pregnancy before the end of the trial, five becoming pregnant within six months of withdrawing (table 1). Thus 281 randomised women had completed a pregnancy.

Seventy five women withdrew from the trial for the following reasons. Sixty six women said that they were no longer interested in a further pregnancy. The reasons given were: family or marital problems (n=7), fear of recurrence (n=7), advanced maternal age (n=4), and medical problems such as hysterectomy (n=5), infertility (n=5), and other medical problems (n=12). Twenty six gave no specific reason. Side effects of the study treatments were mentioned by two women. Four women had to be withdrawn from the study because they wanted to take Pregnavite Forte F. There were no significant differences between the randomised groups in reasons for withdrawal. Three women who could not be contacted for compliance visits eventually had to be withdrawn from the trial and were lost to follow up.

The outcomes of the first pregnancy in the trial for randomised women and the non-randomised control pregnancies are shown in table 2. Sixteen of the 25 spontaneous fetal deaths were examined by a pathologist and it was possible to determine the presence or absence of NTDs in two cases (that is, two informative pregnancies); neither case had a NTD. Recurrence rates of NTDs are expressed as proportions of infants/fetuses in informative pregnancies. There was no recurrence of NTDs among the 172 infants/fetuses in the two groups on folic acid compared with a single NTD recurrence (a stillbirth with anencephalus) in the 89 infants/fetuses in the non-folic acid (multivitamin only) group (rate difference 1·1%; 95% CI 0·4 to 2·4%). In the two multivitamin groups the recurrence rate was 1/176 and there was no recurrence in the 85 infants/fetuses in the non-multivitamin (folic acid only) group (rate difference 0·6%; 95% CI −1·0 to 2·2%).

There were three recurrences in the 103 infants/fetuses in the non-randomised controls. The difference in the recurrence rate between the folic acid groups (no recurrence) and these non-randomised controls was significant (rate difference 2·9%; 95% CI 0·4 to 5·4%). Significance was not evident, however, when the non-folic acid group was combined with these non-randomised subjects to give a recurrence of 4/192 (rate difference 2·1%; 95% CI −0·1 to 4·2%). There were two stillbirths (anencephalus and a baby with polycystic kidneys and cleft lip) in the multivitamin group (2/96=2·1% of all infants/fetuses) and none in the folic acid groups (0/189) (rate difference 2·1%; 95% CI 0·03 to 4·2%). Other fetal and neonatal outcomes are presented in the appendix.

Discussion

The purpose of this trial was to examine the

Table 1 *Baseline characteristics and pregnancy status at end of trial for trial and non-randomised control groups*

	Randomisation group				*Non-randomised controls (n=106)*
	Folic acid (F, n=115)	*Multivitamins (M, n=119)*	*Folic acid plus multivitamins (FM, n=120)*	*All randomised subjects (n=354)*	
Maternal age (years) mean (SD)	31·9 (5·0)	30·6 (4·3)	31·4 (4·5)	31·3 (4·6)	31·3 (5·0)
No (%) married	114 (99·1)	117 (98·3)	118 (98·3)	349 (98·6)	105 (99·1)
No (%) in social classes 5 and 6	22 (19·1)	29 (24·4)	26 (21·6)	77 (21·8)	38 (35·9)[1]
Previous obstetric history					
Mean (SD) No of:					
Births of NTDs	1·07 (0·26)	1·04 (0·24)	1·07 (0·28)	1·06 (0·26)	1·04 (0·19)
Spontaneous abortions	0·63 (1·00)	0·63 (1·06)	0·53 (0·93)	0·59 (1·00)	0·58 (1·14)
Total pregnancies	2·98 (1·78)	2·95 (1·77)	3·03 (1·72)	2·99 (1·75)	3·91 (2·14)[1]
No (%) with spontaneous abortion in immediately preceding pregnancy	20 (17·4)	14 (11·8)	14 (11·7)	48 (13·5)	9 (8·5)
Pregnancy status at close of trial					
No (%) pregnant	93 (80·9)	95 (79·8)	93 (77·5)	281 (79·4)	106
Non-withdrawal	85	93	85	263	
Withdrawal	8	2	8	18	
No (%) not pregnant	22 (19·1)	23 (19·3)	25 (20·8)	70 (19·8)	
Non-withdrawal	4	4	8	16	
Withdrawal	18	19	17	54	
Pregnancy status not known in withdrawals	—	1 (0·9)	2 (1·7)	3 (0·8)	

[1] Randomised subjects v non-randomised controls. p<0·01

Table 2 *Pregnancy outcome in trial and non-randomised control groups*

	Randomisation group				*Non-randomised controls (n=106)*
	Folic acid (F, n=115)	*Multivitamins (M, n=19)*	*Folic acid plus multivitamins (FM, n=120)*	*All randomised subjects (n=354)*	
Informative outcome (total)	85 [1]	89 [1]	87 [2]	261 [4]	103 [3]
No (%) of:					
Livebirths	85 (90·4) [1]	87 (90·6) [1]	85 (89·5) [2]	257 (90·2) [4]	99 (90·8) [3]
Stillbirths	—	2 (2·1)	—	2 (0·7)	4 (3·7)*
Spontaneous abortions	—	—	2 (2·1)	2 (0·7)	—
Non-informative outcome (total)	9	7	8	24	6
No (%) of					
Spontaneous abortions	9 (9·6)	7 (7·3)	7 (7·4)	23 (8·1)	6 (5·5)
Ectopic	—	—	1 (1·0)	1 (0·3)	—
Total No (%) of infants/fetuses	94 (100·0) [1]	96 (100·0) [1]	95 (100·0) [2]	285 (100·0) [4]	109 (100·0) [3]
Total No of pregnancies	93	95	93	281	106
No of women not pregnant	22	23	25	70	—
Pregnancy status unknown	—	1	2	3	—

Unless otherwise stated, the data relate to infants/fetuses resulting from the first pregnancy on the trial. Figures in lower parentheses [ ] indicate numbers of twin pairs included.
No statistically significant differences between randomised groups
*Randomised subjects v non-randomised controls: p<0·05

results of Smithells *et al*[1] using a randomised design. Due to a marked fall over the study period in the number of eligible participants, it became necessary to end the trial prematurely without the initial target number of participants being reached and without a treatment effect being clearly established.

There was one NTD recurrence in this trial which occurred in the non-folic acid group. There were no significant differences in recurrence between the randomised groups. With only one recurrence it is obviously difficult to draw any major conclusions. The difference in the recurrence rate between the folic acid groups and the non-randomised controls was statistically significant ($p=0·02$) but when the multivitamin only group (who did not receive folic acid supplementation) was combined with the non-randomised controls (who probably did not receive folic acid supplementation), the difference just failed to reach statistical significance ($p=0·06$). This analysis is contingent on accepting the appropriateness of the statistical test used (see methods). Furthermore, as this is a comparison between a randomised group and a non-randomised control group, we feel that this finding should be interpreted with great caution. Despite our reservations these results are presented in view of the important question of high versus low dose folic acid in preventing NTDs.[12]

The very low recurrence rate in the randomised women (0·4%) may have been due to self selection into the trial by women with a low recurrence risk. A comparison between the randomised women and the non-randomised controls for the risk factors for recurrence showed no consistent differences between the groups, although the control women had more previous births and were more likely to be in the lower social classes. Other confounding factors not investigated, for example, diet, may have contributed to the difference in recurrence rates. Baseline characteristics were similar for the three randomised groups, however.

Our findings are consistent with those of the MRC trial which demonstrated the efficacy of folic acid in preventing NTD recurrence.[6] The absence of any NTD in the 169 women allocated to folic acid suggests that folic acid may also have been protective in our study. Should this be so, it raises the important consideration that folic acid may be protective at a daily dosage of 0·36 mg as used by us as well as at the much higher dosage of 4 mg used in the MRC trial. In the non-randomised studies conducted by Smithells *et al*,[1, 4] women supplemented with Pregnavite Forte F, which contained a daily dose of 0·36 mg of folic acid, had a consistently low recurrence rate of 1·0% or less. However, the dangers of comparisons with non-randomised studies are well documented. We emphasise that our findings, taken on their own, do not provide clear evidence of a protective effect of either folic acid or other vitamins.

Based on the criteria for registering congenital malformations by the population based Dublin Eurocat Register of congenital malformations and excluding NTDs, 12 (4·6%) of the babies in the randomised groups had one or more congenital malformations compared with 2·8% of babies in the Dublin Eurocat register during 1982–87 ($p=0·08$).[13] A possible explanation for the higher rate in the trial is that ascertainment may have been more complete in these babies. It was interesting to note that women in the non-folic acid group had a higher stillbirth rate which was accounted for by two babies with congenital malformations (including the NTD recurrence).

The MRC trial provides evidence that periconceptional supplementation with folic acid reduces the recurrence risk of NTDs and recommends a daily dose of 4 mg of this substance.[6] We propose that this advice should be offered to Irish women, although we have some reservations at the moment about the need for and safety of this high dose of folic acid.[14] Further research on this and other aspects is in progress.

Appendix

FETAL AND NEONATAL OUTCOMES

Among the randomised women there were 13 infants/fetuses reported as having a congenital malformation excluding the NTD recurrence (a stillbirth with anencephalus) but including the other stillbirth with polycystic kidneys and cleft lip. There were seven major malformations: one in group F (bilateral corneal ectasia with agenesis of the corpus callosum), four in M (polycystic kidneys with cleft lip, congenital mitral insufficiency, polydactyly, and pyloric stenosis), and two in FM (urethral obstruction and cystic fibrosis). Six minor malformations were reported: four cases of congenital dislocation of the hip (one in group F and three in group FM), talipes (group F), and scaphocephaly (group M). Three babies had anomalies of interest in that they might possibly be related to NTDs. One baby in group F had a postanal dimple; a baby in group M had a pilonidal sinus at the base of the lumbar spine and a radiograph showed slight widening of the lumbar spine; a baby in group FM had a sacral naevus without underlying bony defect seen on radiography. Three major congenital malformations were reported in the control group: hydrocephalus (without spina bifida), oesophageal atresia, and transposition of the great vessels. During the neonatal period one baby in group M developed *Escherichia coli* septicaemia and another in group FM had necrotising enterocolitis.

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The coordination centre was the Health Research Board, Dublin, Dr P N Kirke, Ms J Murtagh, Ms P Lawler, Ms B Fitzpatrick, and Ms H Burke

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If children got more calcium

If children and adolescents have a relatively high intake of calcium then peak bone mass (PBM) achieved in early adulthood is likely to be greater.

If PBM is higher, then bone mass in later life is also likely to be higher and fractures in middle and old age less common.

If hip fractures occur in people with osteoporosis there may be an associated mortality of up to 20%.

If children develop a dietary habit it may persist when they are adults.

If people take more exercise, that too leads to them having a greater bone mass.

If the recommended dietary intake of calcium in childhood is increased will it be wholly beneficial.

If children take more calcium they are likely to do so by taking more milk. Would that be entirely a good thing?

If one of a pair of identical twins is given capsules of calcium citrate malate daily for three years and the other twin is given placebo then, provided they remain prepubertal at the end of the three years, the one given extra calcium will achieve a greater bone density (C Conrad Johnston Jr and colleagues, *New England Journal of Medicine* 1992;327:82–7.

If I were a parent of twins I think I'd want to protect them from researchers.

If calcium is present in the human body with the same relative abundance as in the earth's crust and the ratios of the various isotopes of calcium in all things terrestrial were determined 4·5 billion years ago (Velimir Matkovic, leading article, *New England Journal of Medicine* 1992;**327**:119–20) how could anybody top that as a piece of information?

ARCHIVIST

If Rudyard Kipling is looking down from above I'm sure he'll understand

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Immunohistochemical features of the portal tract mononuclear cell infiltrate in chronic aggressive hepatitis

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Abstract

The portal tract mononuclear cell infiltrate has been characterised in 28 liver biopsy samples showing features of chronic aggressive hepatitis from 12 patients with autoimmune chronic active hepatitis, 12 with primary sclerosing cholangitis, and four with other chronic liver diseases (two with α_1-antitrypsin deficiency, one with Wilson's disease, and one with chronic hepatitis B infection). In all patients liver disease had started in childhood. The mononuclear cell infiltrate was investigated by a two step immunoperoxidase technique using monoclonal antibodies to: total, α/β T cell receptor positive, helper/inducer, suppressor/cytotoxic T lymphocytes; B lymphocytes; killer/natural killer cells; monocyte/macrophages; and to the activation markers HLA-DR antigens, interleukin 2 receptor (IL-2R), transferrin receptor, and 4F2Ag. In all samples the infiltrate consisted of mainly α/β T cell receptor T lymphocytes. Although T helper/inducer cells predominated in patients with autoimmune chronic active hepatitis, T suppressor/cytotoxic lymphocytes were preponderant in patients with primary sclerosing cholangitis and the other chronic liver diseases. Killer/natural killer cells accounted for up to 25% of the mononuclear cell infiltrate in patients with autoimmune chronic active hepatitis, being rare or absent in the other diseases. Monocytes/macrophages were always found, but they were more numerous in primary sclerosing cholangitis than in the other chronic liver diseases. B lymphocytes were rare or absent in all subjects. Activated mononuclear cells were present in all subjects, but although in patients with autoimmune chronic active hepatitis and primary sclerosing cholangitis most cells of the infiltrate expressed HLA-DR antigens and up to 75% IL-2R, in other forms of chronic liver diseases HLA-DR positive cells were less common and IL-2R positive cells were rare or absent. These results show that the cells responsible for the histological characteristics of chronic aggressive hepatitis vary in their functional phenotype and state of activation according to the type of underlying liver disorder, confirming the involvement of different pathogenetic mechanisms.

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Mononuclear cell infiltrate and piecemeal necrosis are the histological hallmarks of chronic aggressive hepatitis.[1 2] They are observed in a number of chronic liver diseases of various aetiologies. It is believed that among the infiltrating mononuclear cells are the effectors of piecemeal necrosis and the stimulators of fibrogenesis, which ultimately result in loss of hepatic parenchyma and cirrhosis.[3]

Since monoclonal antibodies have been available for immunohistochemical use, several studies characterising the mononuclear cell infiltrate have been performed in adult patients with different forms of chronic aggressive hepatitis, including autoimmune chronic active hepatitis,[4–6] hepatitis B virus related chronic active hepatitis,[4–10] primary biliary cirrhosis,[4 6 8 11 12] primary sclerosing cholangitis,[11–13] chronic alcoholic hepatitis,[6 14] and non-A-non-B chronic active hepatitis.[10] In childhood, the histological picture of chronic aggressive hepatitis, characteristic of chronic active hepatitis, is also often found in patients with primary sclerosing cholangitis,[15] hepatitis B virus related chronic liver disease,[16] Wilson's disease,[17] and occasionally α_1-antitrypsin deficiency.[18] To date no study characterising the mononuclear cell infiltrate in children with chronic liver diseases has been reported. Moreover, although circulating activated T lymphocytes in various forms of chronic aggressive hepatitis have been considered to be of pathogenic and clinical importance,[19–21] in only three studies has the expression of activation markers on the hepatic mononuclear cell infiltrate been investigated.[8 10 13]

We have characterised the portal tract mononuclear cell infiltrate in liver biopsy samples from children with chronic liver diseases and features of chronic aggressive hepatitis using a panel of monoclonal antibodies directed against markers of function and activation.

Patients, materials, and methods

PATIENTS

Twenty eight subjects (18 female patients; median age 12 years, range 1–20 years) with chronic liver disease starting in childhood and a histological picture of chronic aggressive hepatitis at presentation were studied (tables 1–3). Three of these subjects, all with chronic active hepatitis, were older than 16 years of age (17, 18, and 20 years) at the time of study but were 10, 11, and 13 years old at presentation. Liver disease was considered to be active when the total histopathological score was greater than 3 (see later) or values of aspartate transaminase were more than twice the upper normal value (45 IU/l), or both.

Twelve patients had autoimmune chronic active hepatitis diagnosed according to internationally agreed criteria[22] (table 1). Three were tested before treatment was started and had high values of asparatate transaminase, IgG, non-organ specific autoantibodies, and the presence of piecemeal necrosis in the liver biopsy sample. Seven were tested while receiving immunosuppressive treatment (azathioprine 1–1·5 mg/kg/day and prednisolone 0·5–2 mg/kg/day in six patients; prednisolone 0·5 mg/kg/day in one patient); three had signs of active disease with increased levels of aspartate transaminase, IgG, autoantibodies, and piecemeal necrosis at histology. The remaining four treated patients and two further patients tested during remission in the absence of treatment, had no biochemical, immunological, nor histological evidence of active disease. Three of the 12 children had associated cirrhosis.

Twelve children had primary sclerosing cholangitis (table 2). All had characteristic endoscopic retrograde cholangiopancreatographic changes and 10 had associated inflammatory bowel disease. Three were tested at diagnosis before treatment and nine while receiving treatment (prednisolone 0·5–1 mg/kg/day in five patients; azathioprine 1–1·5 mg/kg/day and prednisolone 0·5 mg/kg/day in two patients; penicillamine 20 mg/kg/day in one patient; sulphasalazine (Salazopyrin, Kabi Pharmacia),

Table 1 Clinical, biochemical, immunological, and histological details of the patients with autoimmune chronic active hepatitis at the time of testing

Patient No	*Sex*	*Age (years)*	*Disease status*	*Immunosuppressive treatment**	*Cirrhosis*	*Portal tract infiltrate†*	*Piecemeal necrosis†*	*Aspartate transaminase (IU/l)‡*	*IgG (g/l)§*	*Autoantibodies¶*		
										ANA	*ASMA*	*LKM1*
1	F	1[illegible]	Active	Pred/aza	Present	2	2	120	23 7	Negative	Negative	Positive
2	F	1[illegible]	Inactive	None	Present	2	1	26	7·3	Positive	Negative	Negative
3	M	2[illegible]	Inactive	Pred/aza	Absent	2	1	53	ND	ND	ND	ND
4	M	13	Inactive	Pred/aza	Absent	2	1	26	11·5	Negative	Negative	Negative
5	M	17	Inactive	Pred/aza	Absent	2	1	24	13·3	Negative	Negative	Positive
6	F	1[illegible]	Inactive	None	Absent	2	1	30	14·2	Negative	Positive	Negative
7	F	1[illegible]	Active	Pred/aza	Absent	3	2	371	19·5	Positive	Negative	Negative
8	F	[illegible]	Active	Pred	Present	3	3	157	20·8	Positive	Positive	Negative
9	F	1[illegible]	Active	None	Absent	4	4	172	50 3	Positive	Negative	Negative
10	F	1[illegible]	Inactive	Pred/aza	Absent	2	1	33	11 7	Negative	Negative	Negative
11	F	6	Active	None	Absent	3	2	1260	19 2	Positive	Negative	Negative
12	F	5	Active	None	Absent	2	2	185	21 8	Negative	Negative	Positive

*Pred=prednisolone, aza=azathioprine.
†Liver biopsy samples were assessed semiquantitatively, as desribed in text
‡Normal values <45 IU/l.
§Normal values for children aged between 2 and 5 years >5–<17 g/l, 5 and 16 years >7–<18 g/l
¶Titres ≥1:40. ANA=antinuclear antibodies, ASMA=smooth muscle antibody, LKM1=liver kidney microsomal antibody type 1.
ND=not determined.

Table 2 Clinical, biochemical, immunological, and histological details of the patients with sclerosing cholangitis at the time of testing

Patient No	*Sex*	*Age (years)*	*Disease status*	*Immunosuppressive treatment**	*Cirrhosis*	*Portal tract infiltrate†*	*Piecemeal necrosis†*	*Aspartate transaminase (IU/l)‡*	*IgG (g/l)§*	*Autoantibodies¶*		
										ANA	*ASMA*	*LKM1*
1	F	10	Active	Pred	Absent	2	1	543	35 1	Positive	Negative	Negative
2	M	8	Active	Pred/aza	Absent	2	1	150	20 4	Positive	Negative	Negative
3	M	7	Inactive	Pred/aza	Present	2	1	47	7 4	Negative	Negative	Negative
4	M	15	Inactive	Pred	Absent	2	1	28	12 5	Positive	Negative	Negative
5	M	12	Active	Penicillamine	Present	2	2	109	18 8	Negative	Positive	Negative
6	F	6	Active	Pred	Absent	3	1	98	12 2	Negative	Positive	Negative
7	F	8	Inactive	Pred	Absent	2	1	34	25·0	Positive	Negative	Negative
8	F	12	Active	Pred	Absent	2	1	218	27 3	Positive	Positive	Negative
9	M	5	Active	None‖	Absent	2	1	197	28 5	Positive	Negative	Negative
10	F	6	Active	None	Present	4	3	352	41·1	Positive	Negative	Negative
11	F	2	Active	None	Present	2	2	110	16 4	Negative	Negative	Negative
12	F	2	Active	None	Present	2	3	740	38·1	Positive	Positive	Negative

*Pred=prednisolone, aza=azathioprine.
†Liver biopsy samples were assessed semiquantitatively, as desribed in text
‡Normal values <45 IU/l
§Normal values for children aged between 2 and 5 years >5–<17 g/l, 5 and 16 years >7–<18 g/l.
¶Titres ≥1:40 ANA=antinuclear antibody; ASMA=smooth muscle antibody, LKM1=liver kidney microsomal antibody type 1.
‖Patient discontinued treatment
ND=not determined

Table 3 Clinical, biochemical, immunological, and histological details of the patients with other forms of chronic aggressive hepatitis

*Patient No (diagnosis)**	*Sex*	*Age (years)*	*Disease status*	*Immunosuppressive treatment**	*Cirrhosis*	*Portal tract infiltrate†*	*Piecemeal necrosis†*	*Aspartate transaminase (IU/l)‡*	*IgG (g/l)§*	*Autoantibodies¶*		
										ANA	*ASMA*	*LKM1*
1 (A1ATD)	M	1	Active	None	Present	2	2	147	ND	ND	ND	ND
2 (A1ATD)	F	12	Active	None	Present	3	3	142	12 5	Negative	Negative	Negative
3 (WD)	M	9	Active	None	Present	3	3	490	ND	ND	ND	ND
4 (HBV)	F	5	Active	None	Absent	3	1	24	16 7	Negative	Negative	Negative

*A1ATD=α_1-antitrypsin deficiency, WD=Wilson's disease, and HBV=hepatitis B virus
†Liver biopsy samples were assessed semiquantitatively, as described in text
‡Normal values <45 IU/l
§Normal values for children aged between 2 and 5 years >5–<17 g/l, 5 and 16 years >7–<18 g/l
¶Titres ≥1:40 ANA=antinuclear antibody, ASMA=smooth muscle antibody; LKM1=liver kidney microsomal antibody type 1.
ND=not determined.

30 mg/kg/day in 10 patients), though in one patient treatment had been discontinued for some time by his parents. The three patients tested at diagnosis had active disease with piecemeal necrosis in the liver biopsy sample. The patient who had interrupted treatment and five of the treated patients also had signs of active disease with increased levels of aspartate transaminase, IgG, and non-organ specific autoantibodies, and one had piecemeal necrosis. The three remaining patients, all receiving treatment, had no clinical, immunological, nor histological evidence of active disease. Cirrhosis was present in five patients.

Four children had other forms of chronic aggressive hepatitis (table 3): two had α_1-antitrypsin deficiency, one had Wilson's disease, and one had hepatitis B surface antigen (HBsAg)/hepatitis B e antigen (HBeAg) positive chronic active hepatitis. None of these patients was receiving immunosuppressive or antiviral treatment. All had signs of active disease and cirrhosis was present in three patients. These children were selected because their liver biopsy samples showed degrees of portal tract infiltration and piecemeal necrosis similar to those observed in chronic active hepatitis and primary sclerosing cholangitis.

BIOPSY SAMPLES

Liver tissue was obtained for diagnostic or management purposes using a 1·4 mm diameter Menghini needle. Informed consent for the liver biopsy was given by the parents of all children. Three to five millimetres of each biopsy sample were embedded in OCT medium (BDH, Poole, UK) and immediately stored in liquid nitrogen before immunohistochemical analysis; most of the specimen was fixed in formalin and processed for routine diagnostic histopathological examination. Liver biopsy samples were assessed for portal tract infiltration and piecemeal necrosis using a semiquantitative scale according to Scheuer[23] (none=1, mild=2, moderate=3, severe=4).

IMMUNOLOGICAL REAGENTS

Most of the monoclonal antibodies (table 4) used in this study were purified by protein A or ion exchange chromatography from the supernatant or the ascitic fluid of hybridoma (American Type Culture Collection, Rockville) cultures in vitro or in vivo respectively. WT31 was purchased from Becton Dickinson. The monoclonal antibody BE3F9 (American Type Culture Collection) directed to bovine insulin was used as control.

Table 4 Monoclonal antibodies used in this study

Monoclonal antibody	*Antigen*	*PBMC subset*	*Dilution*
OKT3	CD3	Total T lymphocytes	1/10
WT31	TCR1	α/β T lymphocytes	1/10
OKT4	CD4	h/i T lymphocytes	1/10
OKT8	CD8	s/c T lymphocytes	1/10
THB5	CD21	B lymphocytes	1/5
OKM1	CD11b	Monocytes/macrophages	1/5
L243	HLA-DR	Activated T and B lymphocytes Monocytes/macrophages	1/160
Anti-Tac	CD25 (IL-2R)	Activated T lymphocytes	1/10
B73.1	CD16	K/NK lymphocytes	1/10
OKT9	CD71 (TFR)	Activated lymphocytes	1/10
4F2	4F2Ag	Activated lymphocytes	1/10
W6/32	HLA-A,B,C	All PBMC	1/160
BE3F9	Bovine insulin	—	1/2

Abbreviations: PBMC=peripheral blood mononuclear cells, CD=cluster of differentiation, TCR=T cell receptor, IL-2R=interleukin 2 receptor; TFR=transferrin receptor, h/i=helper/inducer; s/c=suppressor/cytotoxic, K=killer, and NK=natural killer

Peroxidase conjugated rabbit antimouse immunoglobulin antiserum (Dakopatts, High Wycombe) was used to label the monoclonal antibodies in a two step immunoperoxidase technique. Immunological reagents were used at saturating concentrations, as determined in preliminary titration experiments using normal lymphoid tissue.

STAINING PROCEDURE

The biopsy samples were cut in a cryostat (Bright, Huntingdon) and 5 μm thick sections were obtained and placed on to slides which had previously been coated with a 0·01% solution of poly-L-lysine and allowed to dry.

Sections were allowed to air dry for four to six hours, fixed in a 1:1 mixture of acetone and chloroform for 10 minutes and washed in three changes of phosphate buffered saline (pH 7·4) for five minutes each.

To block the endogenous peroxidase, sections were covered with a 1% solution of hydrogen peroxide in phosphate buffered saline for 20 minutes. After washing, to block non-specific binding, sections were incubated for 10 minutes with phosphate buffered saline containing 10% normal rabbit serum and then incubated for 30 minutes with a dilution in phosphate buffered saline of the respective monoclonal antibody. Sections were washed again and incubated with a 5% dilution in phosphate buffered saline of peroxidase conjugated rabbit antimouse immunoglobulin, which contained 5% normal AB serum, to prevent possible cross reactions between the monoclonal antibodies and human immunoglobulin present on the tissue section. Sections were then washed, immersed for eight minutes in a solution of 0·6 mg/ml of diaminobenzidine tetrahydrochloride and 0·03% hydrogen peroxide in phosphate buffered saline, rinsed in tap water, counterstained with Mayer's haematoxylin, washed again extensively in tap water, and finally mounted with a 9:1 mixture of glycerol and phosphate buffered saline.[24]

MICROSCOPIC ANALYSIS

Stained and unstained mononuclear cells in one to three portal tracts were counted using light microscopy by an observer unaware of the clinical details. The percentage of positive cells was calculated and expressed semiquantitatively, with 0=no positive cells, 1=minimal (<10%), 2=mild (>10%, <25%), 3=moderate (>25%, <50%), 4=abundant (>50%, <75%), and 5=very abundant (>75%) amounts of positive cells.

STATISTICAL ANALYSIS

Positivety scores and the CD4: CD8 ratios were statistically analysed using Wilcoxon's rank sum test and Spearman's rank correlation method.

Results

Stained liver sections were well preserved and tissue structures were easily recognisable. The amount of the mononuclear cell infiltrate in the portal tracts was more abundant in patients with active than inactive disease irrespective of treatment. No positive staining was observed using the control monoclonal antibodies, whereas positive cells labelled by the relevant monoclonal antibodies were identified by the reaction product deposited along their membranes. The amounts of mononuclear cell subsets in portal tracts are given in table 5. Although the numbers of cells varied proportionally with the magnitude of the cellular infiltrate, the tissue distribution of the cells belonging to a particular subset tended to be constant within a given disease.

Results obtained using the monoclonal antibody WT31 were similar to those obtained with OKT3, suggesting the existence of a homogeneous mononuclear cell subset simultaneously bearing T cell receptor 1 and CD3. T Lymphocytes (CD3 positive cells) were the most common infiltrating element in all disorders. When they were subtyped, helper/inducer T cells (CD4 positive) were the most common in autoimmune chronic active hepatitis, were as numerous as suppressor/cytotoxic T cells (CD8 positive) in primary sclerosing cholangitis, and were in a minority in the other forms of chronic aggressive hepatitis, in which suppressor/cytotoxic T cells were almost the only lymphocytes present. The CD4 to CD8 ratio was significantly higher in biopsy samples from patients with autoimmune chronic active hepatitis than in those from children with primary sclerosing cholangitis ($p<0{\cdot}05$) and in the latter it was higher compared with those from patients with other forms of chronic aggressive hepatitis ($p<0{\cdot}01$). Independent of diagnosis, helper/inducer T cells tended to occupy the central areas of the portal tracts (fig 1), whereas suppressor/cytotoxic T cells formed the majority in areas of piecemeal necrosis and could often be observed at the front of the infiltrate invading the hepatic lobule (fig 2). In contrast with helper/inducer T cells, which tended to remain confined within the portal tract, suppressor/cytotoxic T cells could also be identified throughout the lobule, occupying perisinusoidal positions.

B lymphocytes (CD21 positive cells) were rarely or never found in the liver mononuclear cell infiltrate. In follicle-like lymphoid aggregates observed in the portal tracts from two patients with autoimmune chronic active hepatitis, three with primary sclerosing cholangitis, and one with α_1-antitrypsin deficiency, however, B cells represented the main constituents and also displayed the receptors for transferrin and interleukin 2 (fig 3).

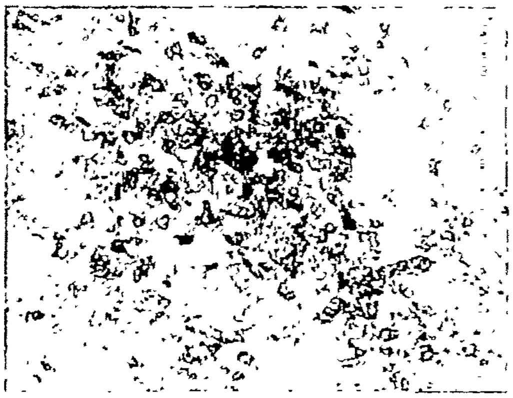

Figure 1 Liver section from a patient with autoimmune chronic active hepatitis stained for the CD8 molecule (suppressor/cytotoxic T lymphocytes). (Immunoperoxidase stain×200.)

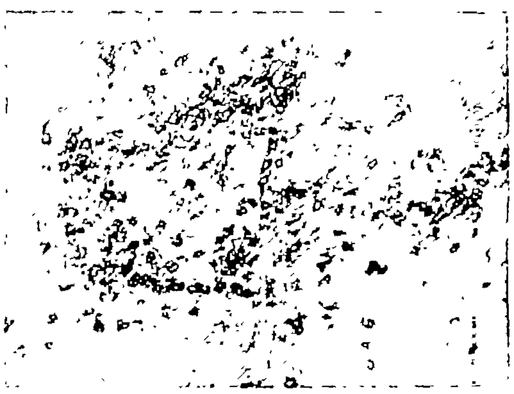

Figure 2 Liver section from a patient with primary sclerosing cholangitis stained for the CD8 molecule (suppressor/cytotoxic T lymphocytes). Positively stained suppressor/cytotoxic T cells project inside the hepatic lobule. (Immunoperoxidase stain×200.)

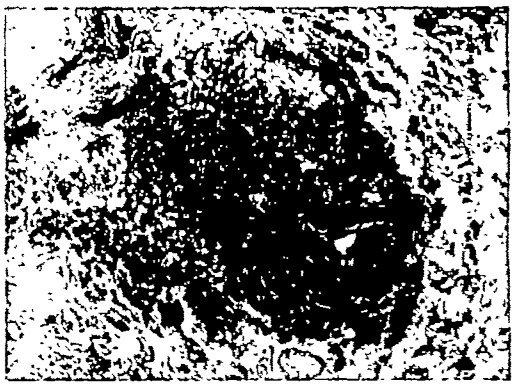

Figure 3 Liver section from a patient with autoimmune chronic active hepatitis stained for the CD21 molecule (B-lymphocytes). B Cells are positively stained in a follicle-like structure in a portal tract. (Immunoperoxidase stain×200.)

Table 5 Median (range) of positivity scores and CD4 CD8 ratios of portal tract mononuclear cell subsets in patients with autoimmune chronic active hepatitis, primary sclerosing cholangitis, or other forms of chronic active hepatitis

	Autoimmune chronic active hepatitis[1]	Primary sclerosing cholangitis	Other forms of chronic active hepatitis[1]
Function markers			
CD3	4·5 (4–5)	4·0 (4–5)	4·0 (4–5)
TCR1	4·5 (4–5)	4·0 (4–5)	4·0 (4–5)
CD4	3·5 (3–4)	3·0 (2–4)	1·0 (1–1)
CD8	2·5 (1–3)	3·0 (2–4)	4·0 (4–5)
CD4·CD8	2·1 (1–4)	1·0 (0·5–1·5)	0·1 (0·1–0·2)
CD21	0 (0–1)	0	0 (0–1)
CD16	2·0 (1–2)	1·0 (0–1)	1·0 (0–1)
CD11b	1·0 (1–1)	3·0 (1–3)	2·5 (1–3)
Activation markers			
HLA-DR	5·0 (4–5)	4·0 (4–5)	4·0 (2–4)
CD25 (IL2R)	3·0 (1–5)	3·0 (1–4)	1·0 (0–2)
CD71 (TFR)	4·0 (2–5)	3·0 (2–5)	3·0 (3–4)
4F2Ag	3·0 (2–5)	3·0 (2–5)	2·0 (1–3)

[1] Number of positive cells: 0=none, 1=<10% 2=>10%, <25%, 3=>25%, <50%, 4=>50%, <75%; 5=>75%.

Killer/natural killer cells (CD16 positive) were the more numerous subset in patients with autoimmune chronic active hepatitis after T lymphocytes, being present in all patients and forming up to a quarter of the mononuclear cell infiltrate. Occasionally they could also be seen scattered within the liver lobule, with a pattern of distribution similar to that described for suppressor/cytotoxic T cells. In patients with primary sclerosing cholangitis and the other forms of chronic aggressive hepatitis they were rare or absent.

Monocytic cells (CD11b positive) were found in all patients, but they were relatively more numerous in patients with primary sclerosing cholangitis, α_1-antitrypsin deficiency, Wilson's disease, and hepatitis B virus related chronic active hepatitis than in autoimmune chronic active hepatitis, in which they were a rare, though consistent, finding.

Mononuclear cells expressing markers of activation were detected in all patients. HLA-DR was the activation marker most often encountered, and in all patients with autoimmune chronic active hepatitis and primary sclerosing cholangitis it was expressed on most of the mononuclear cell infiltrate. IL-2R (CD25) was also found on the mononuclear cell infiltrate in all patients with autoimmune chronic active hepatitis and primary sclerosing cholangitis (fig 4), the number of positive cells ranging from minimal to abundant, although it was a rare finding in the other forms of chronic aggressive hepatitis. Transferrin receptors (CD71) and the antigens targeted by 4F2 (4F2Ag) were found in all patients with chronic aggressive hepatitis investigated without variations among different forms of the disease.

The numbers of cells displaying activation markers varied widely among patients, especially those with autoimmune chronic active hepatitis and primary sclerosing cholangitis. Untreated patients with either autoimmune chronic active hepatitis or primary sclerosing cholangitis tended to have scores of cells positive for activation markers higher than those receiving treatment; this difference was statistically significant for IL-2R ($p<0{\cdot}04$ and $p<0{\cdot}02$ respectively) (fig 5). Scores of positive cells tended to parallel the activity of the disease and the extent of portal tract infiltrate and piecemeal necrosis, but they were not affected by the presence or absence of cirrhosis.

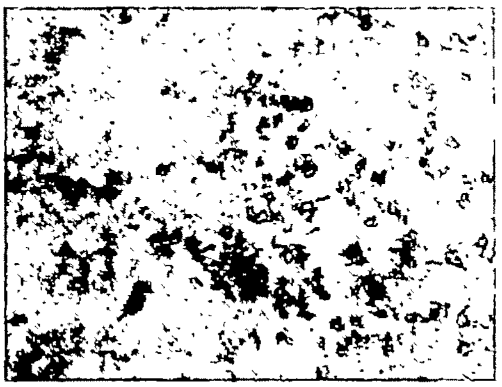

Figure 4 Liver section from a patient with primary sclerosing cholangitis stained for the CD25 molecule. Positive cells are seen in the portal tract (Immunoperoxidase stain×200.)

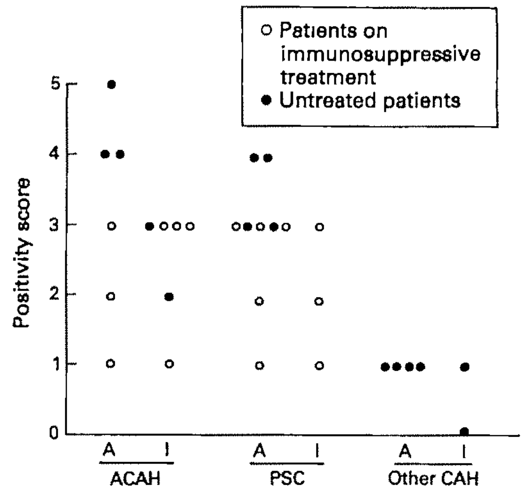

Figure 5 Positivity scores for the CD25 molecule in the patient groups divided according to active and inactive disease. ACAH=autoimmune chronic active hepatitis; PSC=primary sclerosing cholangitis, Other CAH=other forms of chronic aggressive hepatitis, A=active, I=inactive.

Discussion

This study shows that T lympocytes predominate in the portal tract infiltrate of children with various forms of chronic aggressive hepatitis, but the distribution of their markers of function and activation differs according to diagnosis.

Two major patterns of mononuclear cell infiltrate were observed: one typical of autoimmune chronic active hepatitis (characterised by helper/inducer T cells outnumbering suppressor/cytotoxic T cells, a small amount of killer/natural killer cells and a high proportion of activated cells) and one typical of primary sclerosing cholangitis (characterised by similar amounts of helper/inducer and suppressor/cytotoxic T cells, mild to moderate amounts of monocytes/macrophages, with most cells being activated). In the chronic aggressive hepatitis due to α_1-antitrypsin deficiency, Wilson's disease, or chronic hepatitis B infection we observed abundant suppressor/cytotoxic T cells prevailing over helper/inducer T cells and rarer cells expressing IL-2R.

Independent of the cause of chronic aggressive hepatitis or disease activity, akin to observations in adults,[4–7 9 10 12 13] T lymphocytes were the major component of the portal tract mononuclear cell infiltrate in all the children studied. In addition, we have found that the infiltrating T cells expressed mainly T cell receptor 1. Further studies using monoclonal antibodies directed against the γ σ T cell receptor[25 26] will elucidate the presence of T cell receptor 2 positive T lymphocytes.

T cells expressing the suppressor/cytotoxic phenotype were similarly represented in all patients and were concentrated at the periphery of the portal tract and in areas of piecemeal necrosis. This distribution suggests that these cells are cytotoxic lymphocytes and mediate the liver cell damage typical of chronic aggressive hepatitis, irrespective of its aetiology. In contrast with suppressor/cytotoxic T cells, the proportion of helper/inducer T cells was markedly different in the various groups of patients with chronic aggressive hepatitis studied. Similar to observations in adults,[5 6 12 13] numerous CD4 positive T lymphocytes were found in the biopsy samples from children with autoimmune chronic active hepatitis and primary sclerosing cholangitis, being especially abundant in the former. Independent of diagnosis, these regulatory lymphocytes were particularly prominent in the centre of the portal tracts, suggesting that they may orchestrate local immune reactions, through antigen recognition, activation of cytotoxic T cells, B lymphocytes and macrophages, and cytokine production.[27] It is also possible that some of them may modulate tissue damaging immune reactions, as CD4 positive T lymphocytes can act as suppressor cells.[28] In contrast with the results in autoimmune chronic active hepatitis and primary sclerosing cholangitis, CD4 positive cells were present in small numbers in children with other forms of chronic aggressive hepatitis.

The CD4:CD8 ratio was significantly higher in patients with autoimmune chronic active hepatitis than in those with primary sclerosing cholangitis and in the latter when compared with the other forms of chronic aggressive hepatitis. This finding is similar to those obtained in a number of studies of adults[5 6 12 13] and suggests that the CD4:CD8 ratio in the portal tract mononuclear cell infiltrate in liver biopsy samples with features of chronic aggressive hepatitis could be of diagnostic value. The CD4:CD8 ratio of greater than unity observed in the liver in autoimmune chronic active hepatitis reflects the CD4:CD8 ratio of the activated T lymphocytes in the peripheral blood of children with this disease.[20] Similarly, the CD4:CD8 ratio of the infiltrate in patients with primary sclerosing cholangitis parallels the ratio observed within activated T cells in the peripheral blood.[21]

B lymphocytes were seen at low levels or not at all, whatever the cause of chronic aggressive hepatitis. This observation is surprising because of the high immunoglobulin production and the high titres of liver and non-liver specific autoantibodies which characterise diseases such as autoimmune chronic active hepatitis and primary sclerosing cholangitis. In four biopsy samples, however, including two patients with autoimmune chronic active hepatitis and one with primary sclerosing cholangitis, B lymphocytes were observed in follicle-like structures present within some portal tracts, confirming a similar finding reported previously.[29] These structures appear to be unevenly distributed and may have been absent in the other biopsy samples, owing to the small amount of tissue studied. Such an organisation of rudimentary lymphoid tissue within the liver is likely to be a consequence of intense cytokine stimulation in the portal tracts, and this view is supported by evidence that the B cells observed in these structures expressed activation markers.

Killer/natural killer cells, though not numerous, were the most common subset after T lymphocytes in autoimmune chronic active hepatitis, whereas they were rare or absent in the other disorders. This observation reinforces the idea that non-major histocompatibility complex restricted cytotoxicity, including antibody dependent cell mediated cytotoxicity, is likely to be of importance in the development of liver injury in autoimmune chronic active hepatitis.[30 31]

Monocytic cells were always identified, but though they were rare in patients with autoimmune chronic active hepatitis, they were found in small or moderate numbers in patients with primary sclerosing cholangitis and the other forms of chronic aggressive hepatitis, in which they could be involved in the generation of tissue damage, possibly by effecting antibody dependent cell mediated cytotoxicity.[32]

In autoimmune chronic active hepatitis and primary sclerosing cholangitis most mononuclear cells infiltrating the portal tracts displayed activation markers, indicating that they actively affect the immune response. The finding that reduced activation marker expression occurred with treatment and in inactive disease also supports this conclusion. This observation is consistent with the results obtained by measuring IL-2R positive T lymphocytes and soluble IL-2R in the peripheral blood of treated and untreated children with autoimmune chronic active hepatitis.[20 33] Interestingly, in patients with primary sclerosing cholangitis the proportion of peripheral blood T lymphocytes expressing IL-2R is markedly lower than in autoimmune chronic active hepatitis, irrespective of disease activity,[20] though the proportion of these cells in the portal tract inflammatory infiltrate is as high as in autoimmune chronic active hepatitis. This finding may reflect a more generalised autoimmune reaction in autoimmune chronic active hepatitis, where some of the peripheral IL-2R positive T cells may be sensitised to tissues other than the liver.

In conclusion, this study shows the existence of different patterns of expression of markers of function and activation in the portal tract mononuclear cell infiltrate in patients with autoimmune chronic active hepatitis and primary sclerosing cholangitis, and corroborates our previous observations on peripheral blood mononuclear cells,[21] suggesting that despite the clinical and histological similarities the mechanisms leading to autoimmune liver damage in these two diseases are different.

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Bronchial responsiveness and lung function in infants with lower respiratory tract illness over the first six months of life

Jane R Clarke, Amanda Reese, Michael Silverman

Abstract

The aim of this study was to determine whether increased bronchial responsiveness to histamine is associated with lower respiratory tract illness (one or more episodes of wheeze or cough, or both) in infancy.

Fifty four normal newborn infants who had at least one atopic parent were recruited. At a median age of 6·5 months, 45 infants, 23 with a history of lower respiratory tract illness, and 22 without, underwent pulmonary function testing during a symptom free period. The maximum flow at functional residual capacity ($\dot{V}$maxFRC) was calculated from partial forced expiratory flow volume curves using the squeeze technique. Bronchial responsiveness to increasing doses of histamine was assessed by determining the provoking concentration which caused a 30% decrease in $\dot{V}$maxFRC (PC_{30}).

The length adjusted $\dot{V}$maxFRC was lower for symptomatic infants before the challenge (median 125 ml/s; 95% confidence intervals (CI) 85 to 164 ml/s) compared with control infants (median 215 ml/s; 95% CI 159 to 298 ml/s). There was no significant difference in PC_{30} between symptomatic infants (median 10·3 g/l; 95% CI 2·8 to 23·8 g/l) and control infants (median 16·5 g/l; 95% CI 2·4 to 27·9 g/l).

Bronchial responsiveness to histamine can be shown in most infants early in life and is independent of lower respiratory tract symptoms including wheezing.

(*Arch Dis Child* 1992;67:1454–8)

In groups of schoolchildren and adults there is an association between increased bronchial responsiveness and asthma,[1–4] though in individual subjects variations in bronchial responsiveness correlate poorly with the clinical manifestations of asthma[5–7] and with airway calibre at the time of testing.[8 9] Bronchial responsiveness has been shown in infancy in recurrently wheezy subjects[10 11] and in small groups of normal infants.[12–14]

Until recently little was known about the relation of bronchial responsiveness to wheezing in infancy. In one small study of recurrently wheezy infants it was shown that, in contrast with older subjects, bronchial responsiveness in infancy is independent of wheezing, but may be dependent on airway calibre.[15]

The aim of this study was to determine whether the airways of infants with lower respiratory tract illness (one or more episodes of wheeze or cough, or both) were more responsive to histamine than those of asymptomatic control subjects.

Subjects and methods

SUBJECTS

All 45 infants in this study were recruited in the neonatal period from Hammersmith Hospital or Queen Charlotte's and Chelsea Hospital, and were followed up as part of a cohort study. Of the 54 subjects who had originally been recruited, two had moved away from the area by the age of 6 months and seven no longer wished to take part in lung function tests. All members of the cohort had at least one atopic parent, but had otherwise been normal healthy term infants. Infants were classified according to the presence or absence of one or more episodes of cough or wheezing, or both (henceforth referred to as lower respiratory tract illness). Parents were interviewed and details of any recurrent cough or wheezing, or both, since birth were recorded, in addition to a detailed family history including smoking.

At the time of study at the age of 6 months, all infants had been free of respiratory symptoms for at least two weeks. None was receiving any drugs known to affect bronchial responsiveness. Infants were studied after sedation with chloral hydrate (100 mg/kg) or the equivalent dose of triclofos sodium (167 mg/kg). The study was approved by the hospital's ethics committee and parental consent was always obtained. Parents generally stayed in the laboratory during studies.

LUNG FUNCTION

Partial expiratory flow volume curves were obtained using the squeeze technique by rapidly inflating a snugly fitting, polythene thoracoabdominal jacket (medical engineering department, Royal Postgraduate Medical School, Hammersmith Hospital, London), with the arms enclosed, at the end of tidal inspiration to induce a forced expiration.[16 17] The jacket inflation pressure was measured with a pressure transducer (Validyne MP45). From occlusion tests at the end of inspiration the static pressure transmission to the pleural space with this jacket is 56–80% of the applied pressure.[18] Flow was recorded with a low resistance screen pneumotachograph (medical engineering department, Royal Postgraduate Medical School) and facemask (Rendell-Baker Soucek, size 1, Ambu International), connected to a pressure transducer (Validyne MP45). A rim of silicone putty (Carters) was applied around the

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mouth and nose and to the facemask to provide an airtight seal. The flow signal was electronically integrated with respect to time to give the volume. All signals were digitised (100 Hz) and stored on a computer (Compaq deskpro 386/20e). Partial expiratory flow volume curves were constructed by computer and analysed (RASP Software, Physiologic Ltd) to determine the maximum flow at a lung volume corresponding to the functional residual capacity (V̇maxFRC).[19] During baseline measurements the jacket pressure was increased from 25 cm H_2O by increments of 5 cm H_2O until flow limitation had been achieved, as shown by the maximum flow at functional residual capacity, or until the maximum jacket pressure of 80 cm H_2O had been achieved. A mean baseline value of V̇maxFRC was derived from eight to 10 baseline measurements made at the optimal jacket pressure. Thereafter the same jacket pressure was used throughout the challenge test procedure.

The shape of the baseline partial expiratory flow volume curves was described qualitatively for each subject, as either concave or convex with respect to the origin.

HISTAMINE CHALLENGE

Aerosols of normal saline, as a control, and doubling concentrations of histamine were administered for 30 seconds each by a Wright nebuliser, with 8 l/min airflow (nebuliser output 0·16 ml/min by weighing, aerosol aerodynamic mass median diameter 1·0–1·5 μm[20]). The facemask, pneumotachograph removed, acted as a chamber into which the aerosol was directed over the mouth and nose of the sleeping infant. Beginning with 0·25 g/l, doubling concentrations of histamine were administered at five minute intervals until either a 30% decrease from baseline V̇maxFRC had been observed or the maximum histamine concentration of 32 g/l had been reached. Beginning one minute after completion of each nebulisation, six to 10 squeeze manoeuvres were then carried out. All technically satisfactory curves were analysed to give a mean V̇maxFRC for each dose. As a safety measure, oxygen saturation (SaO_2) (Ohmeda Biox 3740 pulse oximeter), transcutaneous oxygen tension ($PtcO_2$) and carbon dioxide tension ($PtcCO_2$; Radiometer TCM3, Radiometer) were monitored continuously.

The provoking concentration of histamine producing a 30% decrease in V̇maxFRC (PC$_{30}$) from baseline was obtained by linear interpolation from dose-response plots of V̇maxFRC against log histamine concentration for each subject.

ANALYSIS

The lengths, weights, and ages of the infants with and without lower respiratory tract illness were compared using Student's *t* tests. The gender distribution, ethnic origin, and history of maternal smoking in the two groups were compared using a χ^2 test with Yates's correction. V̇maxFRC was adjusted to a length of 70 cm using regression equations derived from the normal subjects in the cohort. For normal male subjects, V̇maxFRC (ml/s)=6·97 (length in cm) −244, and for female subjects V̇maxFRC (ml/s)=8·07 (length in cm) −270. For female subjects length adjusted V̇maxFRC was further adjusted for gender from the regression equations (by multiplying by 0·822) to group male and female subjects together for comparison. The V̇maxFRC jacket pressure, and coefficient of variation data were skewed, and the PC$_{30}$ data censored, so they were compared using the Mann-Whitney U test. Values were expressed as medians, with 95% confidence intervals (CI) and interquartile ranges. The study design allowed a difference of two doubling concentrations in PC$_{30}$ (boys and girls grouped together) and a 120 ml/s difference in length adjusted V̇maxFRC (boys and girls compared separately) to be detected between the normal and symptomatic groups, with a power of greater than 80% at a significance level of 5%.

Results

There were similar numbers of boys and girls in the study (23/22), but more boys than girls had developed symptoms by 6 months of age (13/10). Of those with lower respiratory tract illness, seven symptomatic boys and six symptomatic girls had coughed without any wheeze. Of the four boys and five girls from the original birth cohort of 54 infants who dropped out of the study, two boys and two girls had developed symptoms by 6 months. The ages and lengths of the infants with lower respiratory tract illness and control infants were similar, but the symptomatic male infants were significantly heavier than the normal boys ($p<0·05$). There was no significant difference in the numbers of maternal smokers or non-white subjects between the two groups (table 1) or of other family members who smoked. Further analysis into the independent effect of parental smoking on lung function was precluded because of the small number of subjects.

Table 1 Baseline data. Mean (range) or number (%) are given

Characteristic	*Boys*			*Girls*		
	*LRI** *(n=13)*	*No LRI** *(n=10)*	*p Value†*	*LRI** *(n=10)*	*No LRI** *(n=12)*	*p Value†*
Age (months)	6·65 (5·5–8·0)	6·45 (6·0–8·0)	0·52	6·60 (6·0–8·0)	6·21 (6·0–7·0)	0·10
Weight (kg)	8·51 (6·92–10·0)	7·74 (6·30–8·74)	0·048	7·73 (5·59–10·0)	7·61 (6·6–10·7)	0·80
Length (cm)	69·3 (66–74)	68·5 (63–72)	0·43	67·8 (63–70)	67·7 (65–73)	0·90
Maternal smokers	4 (31)	1 (10)	0·49	2 (20)	1 (8)	0·70
Non-white subjects	3 (23)	1 (10)	0·79	2 (20)	2 (17)	0·83

*LRI=lower respiratory tract illness

†p Value=significance of difference between subjects with LRI and without LRI (*t* test or χ^2 test).

Table 2 Gender and length adjusted $\dot{V}$maxFRC and P_{30}

	*LRI**	*No LRI**	*p Value*
$\dot{V}$maxFRC (ml/s)			
No of subjects	23	22	
Median	125·4	214·9	0 0001
95% CI	85 0 to 164·2	159 4 to 298 0	
Mean CV (%)	9·9	9·0	0 11
95% CI	8·2 to 11·3	6·1 to 9·4	
PC_{30} (g/l)			
No of subjects	19	20	
Median value	10·3	16·5	0·97
95% CI	2 82 to 23·82	2 35 to 27 86	

*LRI=lower respiratory tract illness, CV=coefficient of variation (within subject).

For both male and female infants the length adjusted $\dot{V}$maxFRC before challenge was significantly lower for the symptomatic group than for the control infants (table 2; fig 1). The median difference in length adjusted $\dot{V}$maxFRC between symptomatic and control infants was 108·0 ml/s for boys (95% CI 45·9 to 251·6 ml/s; p=0·006) and 102·1 ml/s for girls (95% CI 17·8 to 232·2 ml/s; p=0·013). There was no significant difference in repeatability of $\dot{V}$maxFRC expressed as a coefficient of variation between symptomatic and control subjects (table 2).

The median jacket pressure required to produce flow limitation during the squeeze manoeuvre was significantly lower for the group with lower respiratory tract illness than for the control infants (37 *v* 46 cm H_2O respectively; p<0·05). There was no significant difference between symptomatic subjects and controls in the distribution of the shapes of the partial expiratory flow volume curves (concave:convex =16:7 for subjects with lower respiratory tract illness and 12:10 for controls; p=0·46).

Five infants awoke before completing the histamine challenge. During baseline measurements, one male infant from the group with lower respiratory tract illness had flow limited flow volume curves during tidal breathing, precluding histamine challenge. For the remaining infants, (nine control and 11 symptomatic boys; 12 control and seven symptomatic girls), there was no significant difference in PC_{30} between symptomatic infants and normal infants (table 2; figure 2). There was no correlation between length adjusted $\dot{V}$maxFRC before histamine challenge and PC_{30} for the whole study group.

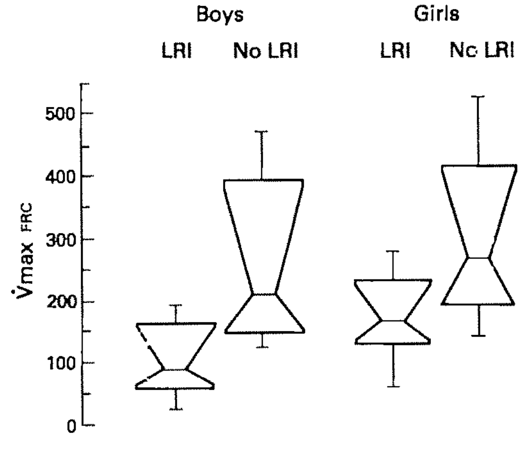

Figure 1 Maximum flow at functional residual capacity ($\dot{V}$maxFRC, ml/s), adjusted for length, for boys and girls with and without lower respiratory tract illness (LRI) The box, notches, and bars indicate median with interquartile range, 95% CI, and range respectively.

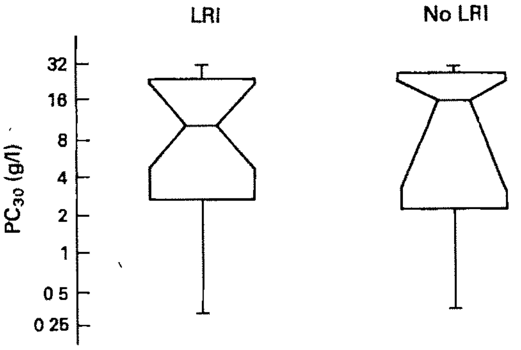

Figure 2 Concentration of histamine which caused a 30% decrease in maximum flow at functional residual capacity (PC_{30}) (g/l) for infants with and without lower respiratory tract illness (LRI). The box, notches, and bars indicate median with interquartile range, 95% CI, and range respectively.

Before histamine challenge, oxygen saturation was greater than 94% for all subjects. During bronchial challenge only four infants desaturated below 90%, the minimum recorded Sao_2 being 83%, with spontaneous recovery. The maximum decrease in $Ptco_2$ from prechallenge recordings was 4·2 kPa; in 11 infants $Ptco_2$ decreased by more than 2 kPa during challenge. There was no significant change in $Ptcco_2$ during histamine challenge.

Discussion

In contrast with reports of an association between bronchial responsiveness and wheezing in older subjects,[1-4] we found no association between bronchial responsiveness to histamine and lower respiratory tract illness in 6 month old infants. Baseline lung function, however, was reduced in symptomatic boys and girls, despite their being free of symptoms at the time of study. Our findings in children of atopic parents are similar to those reported by Stick *et al* in a random sample of the population,[15] using similar methodology.

The baseline measurements of $\dot{V}$maxFRC for the control subjects were similar to those few reference ranges reported for infants.[21 22] All reference data show a wide scatter of size corrected $\dot{V}$maxFRC between subjects, but the method is repeatable within subjects. Doubt has been cast on the assumption that in healthy infants, flow limitation is achieved by the squeeze technique.[23 24] This study does not determine whether the symptomatic infants had lower $\dot{V}$maxFRC before any respiratory illness (that is, whether small airway calibre might have predisposed them to symptomatic lower respiratory tract illness[25 26]), or, alternatively, whether deterioration in previously normal lung function was a consequence of lower respiratory tract illness.

The configuration of the maximum expiratory flow-volume curve is a sensitive index of disturbed pulmonary mechanics, indicating imbalance between peripheral elastic and flow resistive components of the lungs. Minor changes have been interpreted as indicating 'small airway disease'.[27] The similarity in the shape of the partial expiratory flow volume curves in the group with lower respiratory tract illness and control subjects, despite the lower V̇maxFRC in those with lower respiratory tract illness, is compatible with a pre-existing developmental pulmonary anomaly, as shown by Martinez and colleagues,[25 26] rather than 'lung damage'. The configuration of partial expiratory flow-volume curves in infants are, however, at least partly dependent on the external compression applied. Excessive jacket pressures tend to produce increasingly convex curves and a consequent reduction in, V̇maxFRC, sometimes called 'negative pressure dependency of flow'.[18] In our study various jacket pressures were used to determine the optimal pressure at which flow limitation was just achieved.

The squeeze technique does not take account of changes in the level at the end of expiration during bronchial challenge. Assessing bronchial responsiveness from changes in V̇maxFRC may therefore result in an underestimate of response in infants whose functional residual capacity increases during challenge.[28] A difference in the functional residual capacity in response to challenge, between infants with lower respiratory tract illness and controls, could have masked a true difference in PC_{30}.

The levels of bronchial responsiveness to histamine which we found were lower (that is, PC_{30} was higher) than those reported previously.[10 12] Differences between studies in the methodology, especially in the duration of histamine nebulisation and in the type of jet nebuliser used, may be the explanation. The effect of air entrainment on the dose of aerosol delivered to the lungs varies with age,[29] but is unlikely to have been a factor as the infants in the group with lower respiratory tract illness and controls were of similar size and age.

Various factors may influence infant lung function and bronchial responsiveness. An Australian study looking at factors influencing bronchial responsiveness in early infancy showed that infants with either a family history of asthma or of parental smoking had increased levels of bronchial responsiveness at around 1 month of age.[30] There was no difference in baseline V̇maxFRC. In contrast, a more extensive population survey in Boston (USA) showed reduced levels of forced expiratory flow within the first two months of life in infants born to smoking mothers, without a change in the functional residual capacity.[31] They did not assess bronchial responsiveness. There were insufficient numbers of maternal smokers in our study to look at the effect of maternal smoking on baseline lung function or bronchial responsiveness. All of our infants had a parental history of atopy, though neither our subjects nor their parents were tested for atopy.

A prospective study in young adults[32] showed that enhanced bronchial responsiveness usually precedes the development of clinical asthma and is compatible with a genetic basis for it. Epidemiological studies of 7 and 11 year old children have shown that wheeze is not associated with bronchial hyperresponsiveness in the absence of atopy, but is strongly related to bronchial hyperresponsiveness when atopy is present.[33] In a large longitudinal study of 11 year old New Zealand schoolchildren,[34] childhood asthma was shown to be strongly linked to allergy. Bronchial responsiveness correlated significantly with allergy as determined by the serum IgE concentration, even in some children with no clinical features of atopy.

There is reason to believe that the situation may be different in infants and young children, where infantile asthma is essentially a non-atopic illness[35] even among the infants of atopic parents.[36] At the age of 3 years there was no significant difference in bronchial responsiveness between atopic and non-atopic preschool children, all of whom had a history of severe wheeze.[37] It has been suggested that only those wheezy infants who have an atopic predisposition and whose airways become sensitised to aero-allergens will develop asthma in later childhood.[35] A prospective study of the relation between bronchial responsiveness and atopic sensitisation by inhaled allergens would further elucidate this hypothesis.

We suggest that at 6 months of age bronchial responsiveness is present in most infants and does not discriminate between those with and without lower respiratory tract illness. Lower respiratory tract symptoms are associated with reduced airway calibre rather than bronchial responsiveness. Later in childhood bronchial responsiveness may become a more important determinant of wheezing, together with atopy.

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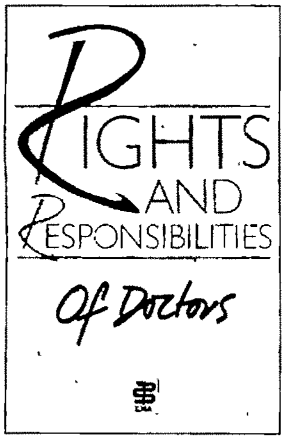

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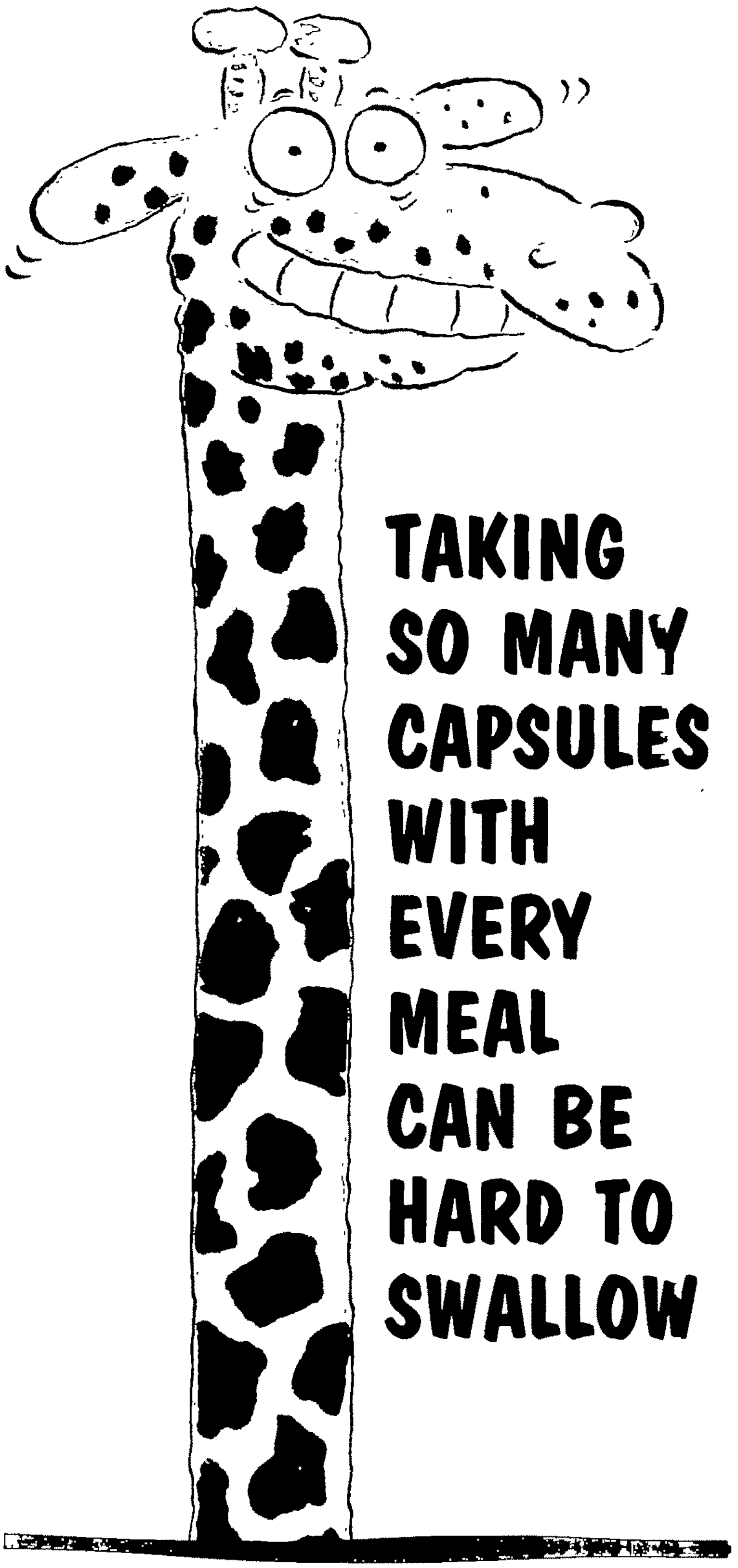

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ntra-indications, warnings, etc: Known hypersensitivity to lamotrigine Cannot yet be recommended renal/hepatic impairment Close monitoring (including hepatic, renal and clotting parameters) of tients who acutely develop any combination of unexplained rash fever flu-like symptoms of lamotrigine In pregnancy the potential benefits must be weighed against any possible risk Withd slowly over 2 weeks to avoid rebound seizures *Side- and adverse effects* In double-blind add clinical trials, skin rashes (usually maculopapular) occurred in 10% of patients taking lamotrigine 5% of patients taking placebo Rash led to withdrawal of lamotrigine in 2% of patients Rarely se skin reactions including angioedema and Stevens-Johnson syndrome have been reported Adv experiences normally associated with standard antiepileptics (including diplopia, dizziness, ata irritability/aggression, etc) have also been reported during trials of Lamictal when added on to therapy (Refer to Data Sheet for further information)

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Association of perinatal events, epilepsy, and central nervous system trauma with juvenile delinquency

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Abstract

The association of perinatal events, childhood epilepsy, and central nervous system trauma with juvenile delinquency was studied prospectively in a geographically defined population of 5966 males in northern Finland. Those who had obtained a criminal record up to the age of 22 years, totalling 355, or 6·0%, were defined as delinquents. The incidence of delinquency was not increased in males with a birth weight less than 2500 g or greater than 4000 g, preterm births <37 weeks' gestation, or those with perinatal brain damage or having epileptic seizures before 14 years of age. The incidence was increased by 6·8% in the group of males with birth weights less than 3500 g, but not significantly increased after standardisation for a number of social and demographic background variables. The incidence was increased by 10·3% among the males who had had a central nervous system trauma by the age of 14 years, however, and this factor remained significant when social and demographic factors were standardised by regression analysis, with an odds ratio of 1·9 for all males with a criminal record and an odds ratio of 3·15 for those who had committed a violent crime. Previous central nervous system trauma may be a cause of delinquency, or another possibility is that the type of behaviour pursued by males who are likely to commit a violent crime will expose them more often to accidents which can result in central nervous system trauma.

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The later development of children with a less favourable perinatal period has been widely investigated with reference to psychomotor, somatic, and mental development, but less interest has been shown in the possible effect of perinatal problems on juvenile delinquency. Causes of delinquency have been sought among social, psychological, and biological factors.[1 2] Perinatal problems such as low birth weight and preterm birth may be followed by behavioural difficulties as an expression of brain damage, and central nervous system trauma and epilepsy during later childhood may be suspected to lead to similar difficulties. We analyse here the association of perinatal and childhood disorders with possible somatic consequences in the brain with juvenile delinquency in prospectively collected data on the northern Finland birth cohort for 1966.[3 4]

Series and methods

The original series consisted of 12 068 pregnant women who gave birth to 12 058 liveborn infants in the two northernmost provinces of Finland in 1966, covering 96% of all births in the area during that year.[3 4] Many social and biological characteristics of the mother and family were recorded during the pregnancy, and also perinatal factors such as birth weight, length of gestation, and perinatal mortality and morbidity after the delivery. The social status of the family and health of the children were recorded with another questionnaire when the children were 14 years old, in 1980 and 1981.[4] A family questionnaire was answered by 96·1% of the families, and the data on school performance and general health for most of the other children were collected from the schools. Only 14 children, 1·2 per thousand, had been lost to follow up by that age. In addition, data on the children's health and development were recorded continuously from birth onwards from various morbidity and mortality registers.[4] Obtainment of a criminal record by the age of 22 years was taken as an indicator of juvenile delinquency The relevant data were collected from the files maintained by the Ministry of Justice for the population aged over 15 years of age and analysed with the other data early in 1989.

A total of 6007 boys and 5757 girls were alive at the age of 15 years, which, after 75 subjects with an intelligence quotient (IQ) less than 5 had been excluded (they had committed no crimes),[5] left 5966 males and 5723 females in the series, of whom 355 males (6·0%) and 4 females (0·7%) had committed at least one crime leading to a criminal record between January 1981 and February 1989. Because of the small number of female offenders, only the data for the males will be considered.

The 355 males were sentenced for 2927 crimes, several sentences often being given concurrently for different crimes—for example, driving an unauthorised motor vehicle without a licence while drunk. The most common crimes were traffic violations, 238 males committing 1097 of these, though 115 of them had also committed crimes of other types. The second most common were crimes involving property, 157 males committing such crimes a total of 1382 times. Violent crimes were taken to include homicides (only three instances), assault, robbery, arson, or violation of domiciliary peace. A total of 104 males committed 239 such crimes. Other types of crime were indiscipline, illegal sale or possession of alcohol or narcotics, and sexual crimes, of which 111 males committed 209. The number of males repeating a crime was 197. The sentence was conditional in 328 instances and unconditional in 84. In addition, 117 males were fined. Thus in many instances the same person had conditional and unconditional sentences and still more often were also fined. Cases which result only in a fine do not constitute a criminal record, with an exception of the rare case of the fine being conditional. There was one such case in this series.

The perinatal factors studied were birth weight <2500 g, <3500 g, and >4000 g, preterm births <37 full gestational weeks, and perinatal brain damage (table). Birth weight was known for all subjects and gestational age for 5757, 96·5% of the total.[4] Children were considered to have perinatal brain damage if they had an Apgar score of 0 at one minute or less than 5 at 15 minutes, convulsions during the neonatal period, or a diagnosis of asphyxia, brain injury, or intraventricular haemorrhage, but did not have central nervous system malformation, chromosomal aberrations, or hereditary central nervous system degeneration.[6] Subjects with epilepsy diagnosed up to the age of 14 years[7] and subjects with central nervous system trauma up to the same age[8] were also analysed. Epilepsy was considered to have been present if there had been at least one episode of paroxysmal disturbance of consciousness, sensation or movement, primarily cerebral in origin and unassociated with acute febrile episodes. Children with febrile convulsions, blank spells, temper tantrums, and transient convulsions occurring in close relation to central nervous system trauma, central nervous system infection, or some other concurrent disorder were not included.[7] The diagnoses regarded as central nervous system traumas were trauma to the skull, cranial fracture, cerebral contusion and concussion, vertebral column trauma if there was also injury to the spinal cord, or trauma to the peripheral nerves. Only subjects admitted to hospital and patients attending an outpatient clinic who underwent a special neurological examination and follow up were included.[8]

The associations between health factors and juvenile delinquency were studied by stepwise logistic regression analysis and the relative risk of delinquency was estimated by the odds ratio (OR) and its 95% confidence interval (CI). Stepwise logistic regression analysis selects the explanatory variables in such a manner that only one of a pair of variables with a high correlation between them is included in the model, for example, of the numerous birthweight variables only that showing the closest association with juvenile delinquency will be included.[9] Many social and demographic factors affecting the family can function as confounding factors and were therefore included in the analyses. These factors were place of residence (urban/rural) and social class of the father at birth, social mobility, and internal migration up to the age of 14 years, maternal schooling, age, and marital status at birth, parental employment, complete versus incomplete family and number of siblings (all at the age of 14 years), desirability of the pregnancy for the mother, maternal smoking during pregnancy, and paternal smoking during childhood. The non-response to the family questionnaire, 3·9% of the subjects, was also seen as a confounding variable and was controlled by the logistic regression analysis. These factors have been described more fully elsewhere.[10]

Results

The table analyses the incidence of delinquency by perinatal events, epilepsy, and central nervous system trauma. Only in the subjects with birth weight <3500 g and those with central nervous system trauma is the incidence statistically significantly increased, by 6·8% for the former group and 10·3% for the latter. Of the 16 subjects with central nervous system trauma and a criminal record, 13 had had concussion, one cerebral contusion, one cerebral contusion and cranial fracture, and one spinal fracture and spinal cord lesion. To study the effect of these biological and health factors on delinquency with the social and demographic background variables standardised, a logistic regression analysis was performed. All the variables presented in the table were included as explanatory variables, together with the social and demographic factors described under methods. The only health factor which had a significant association with delinquency was central nervous system trauma before the age of 14 years, which increased delinquency (OR 1·9, 95% CI 1·09 to 3·30). The social and demographic factors which increased the risk of delinquency were low social class, downward social mobility, one or no parent in the family, urban dwelling, parental smoking, and non-response to the health questionnaire.

Omission of maternal smoking from the explanatory variables did not alter the results—that is, trauma to the central nervous system was significant but not the other health variables.

Number of males with a criminal record by biological and health factors

Biological and health factor	*No of subjects with criminal record*	*All males*	*Incidence of criminal record (%)*	*Difference with respect to others, by χ^2 test (p value)*
Birth weight <2500 g	12	178	6·7	0·651
Birth weight <3500 g	177	2611	6·8	0·017
Birth weight >4000 g	61	1058	5·8	0·778
Preterm birth <37 weeks' gestation*	30	502	6·0	0·972
Firstborn infant	119	1921	6·2	0·598
Born 4th or later in family	66	1052	6·0	0·929
Perinatal brain damage	3	75	4·0	0·472
Epilepsy	5	95	5·3	0·775
Trauma to central nervous system	16	155	10·3	0·020
All subjects	355	5966	6·0	

†Known for 5757 males.

As brain damage has been suspected as a particular cause of violent crimes, two further logistic regression analyses were performed: on males who committed a violent crime and on males who committed some other type of crime. Central nervous system trauma increased the risk in the former analysis (OR 3·15, 95% CI 1·37 to 7·26) but not significantly so in the latter (OR 1·47, 95% CI 0·72 to 2·98). In neither of these analyses was any other health factor significant.

Discussion

Roughly 10% of Finnish males will acquire a criminal record during their lifetime. The main type of crime among males who are sentenced for the first time after adolescence is financial impropriety—for example, infringement of bankruptcy laws or tax evasion. Thus our series with a 6% rate of criminal records includes a substantial number of subjects in this cohort who will commit crimes other than financial crimes. Nevertheless some of the cohort members had committed only a minor crime and will never do so again, but these subjects can be identified only by further follow up surveys.

The boys with a low IQ (<50) were excluded because they were over represented among the subjects with epilepsy and those with perinatal brain damage and can be taken as less 'capable' of juvenile delinquency as measured by a criminal record and are therefore potential confounding elements. Nevertheless, the incidence of delinquency was not increased either in the subjects with epilepsy or in those with perinatal brain damage (table). The incidence of delinquency was statistically significantly increased among the males with a birth weight less than 3500 g, but when the background variables were standardised by logistic regression analysis this significance disappeared, because lower birth weight has an association with factors such as low social status and maternal smoking during pregnancy. A positive association between unfavourable perinatal events and delinquency has been found in some series[11] [12] but not in another.[13] [14] In our series there was clearly no such association.

The association between epilepsy and delinquency, especially that seen in violent crimes, has been widely discussed[15–17] without any clear agreement being reached. Our definition of epilepsy was broad, and many of these males were probably no longer having seizures during adolescence, but it is evident that the group having epileptic seizures during childhood have no particular risk of juvenile delinquency.

Central nervous system trauma was the only health factor which had a statistically significant association with delinquency, especially with that seen in violent crimes, and it remained significant when the data were standardised for many of the background variables. Previous retrospective Finnish surveys have not found such an association.[16] [18] This relation may be causal, but another possibility is that the type of behaviour pursued by males who are likely to commit a violent crime will expose them more often to accidents which can result in central nervous system trauma.

The causes of juvenile delinquency are a complex matter closely related to childhood and adolescent psychiatry, sociology, psychology, neurophysiology, and criminology. We cannot go into the theories and findings in those fields here, but the results show clearly that whatever the reasons for delinquency, they are not mediated through perinatal disorders or childhood epilepsy.

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Archives of Disease in Childhood 1992; 67: 1462–1466

Urinary protein/creatinine index in follow up of patients with Wilms' tumour after nephrectomy

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Abstract

The protein/creatinine index (p/c) was determined in early morning urine (EMU) samples from available patients with Wilms' tumour who had had a nephrectomy and whose diagnosis had been made between January 1970 and December 1989. Clinical details were obtained by case note review. Results were obtained from 36 boys and 40 girls. The mean interval between nephrectomy and measurement of the EMUp/c was 9·0 years (2–23). Eleven patients had a EMUp/c greater than 20 mg/mmol (normal range less than 20). Of the 11 patients with proteinuria, there were in addition to nephrectomy other adverse features including bilateral tumours, treatment with nephrotoxic drugs, and dysplastic kidneys. Renal dysfunction seems most likely to occur where there are adverse factors in addition to unilateral nephrectomy. There was a significant correlation between the glomerular filtration rate and the EMUp/c, and it is thought that this is a simple tool which can be used for the regular monitoring of renal function in these patients.

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The high survival rate for children with Wilms' tumour has raised concern about the ability of the remaining kidney to sustain adequate renal function and allow a normal life span. The main source of concern is the growing number of reports of glomerular hyperfiltration.[1 2] Children with Wilms' tumour invariably lose at least half of their renal mass and therefore need systematic investigation to define the extent of the problem and to identify special risk factors. The need for regular monitoring of these children's renal funtion also raises the issue of how extensively tests should be carried out during follow up.

Patients and methods

Assessment of renal function was carried out between January 1989 and December 1990 for patients receiving long term follow up for Wilms' tumour at The Children's Hospital in Birmingham. Only children whose diagnoses were made between January 1970 and December 1989 were included. Instructions were given to parents about the collection of early morning urine (EMU) samples on the morning that they were due to visit the clinic for review. Particular emphasis was placed on the need for the samples to be collected before the patient was ambulant. Urinary protein/creatinine indices (EMUp/c) were then measured on these samples using the Coomassie blue dye-binding method.[3] The upper limit of normal values for the EMUp/c has been established as 20 mg/mmol.[4] Blood pressure was measured, the diastolic pressure being taken as the point of disappearance of all sounds. Urine was also collected for culture. Estimates of the glomerular filtration rate were made, where creatinine measurements were available, from the formula height×k/plasma creatinine, where k is a constant whose value depends on age and sex.[5] Clearance of chromium-51 labelled EDTA was determined in other patients. The subjects were divided into two groups according to the associated EMUp/c values. Renal biopsy samples were taken from two patients in view of the severity of their disease. A retrospective review of the diagnoses and management details of the patients was carried out using their case notes. The patients were all receiving unrestricted diets, with the exception of two for whom dietary protein intake had been reduced in an attempt to slow down the rate of renal deterioration. There were no documented urinary tract infections at the time of assessment.

Results

Ninety seven urine samples were obtained from 76 patients (36 boys and 40 girls). The mean interval from nephrectomy was 9·0 years (2–23 years). The mean age at nephrectomy was 3·41 years. There was no significant difference in age at nephrectomy between the patients with proteinuria and those without. In 11 patients the EMUp/c was greater than 20 mg/mmol, whereas in 65 patients it was below the upper limit of normal. Sixty four (99%) of the latter had unilateral tumours, and one (2%) had bilateral tumours. Of those with a EMUp/c greater than 20 mg/mmol, seven (64%) had unilateral tumours and four (36%) had bilateral tumours. All patients with a EMUp/c greater than 20 mg/mmol also had positive albustix tests. No haematuria was detected in any of the patients.

RADIOTHERAPY

A total of 42 (55%) patients had received radiotherapy. Thirty one (74%) had received radiation to the renal bed only, seven (17%) had received radiation to the whole abdomen, two (5%) had received radiation to the renal bed and lungs, one (2%) had received radiation to the whole abdomen and lungs, and one (2%) had received radiation to the lungs only.

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The median radiation dose for those children with EMUp/c greater than 20 mg/mmol was 2820 cGy, and that for children with EMUp/c less than 20 mg/mmol was 2000 cGy. However these dose differences were not statistically significant (p>0·05 by Wilcoxon rank sum test). Those patients receiving whole abdominal radiation were equally distrubuted between those with proteinuria and those without (three in each group). Only one patient with bilateral disease received radiotherapy to one renal bed after nephrectomy, but this was stopped after only one fraction (total dose 150 cGy).

BLOOD PRESSURE

Two patients were receiving treatment for hypertension (diastolic blood pressure persistently above the 97th centile for age and sex). These two patients had abnormal renal function and their blood pressures had been normal before the deterioration in renal function. They had had bilateral tumours, one of them also having underlying multicystic kidney disease. The blood pressure results were expressed as SD scores. These were derived from the Report of the Second Task Force on Blood Pressure Control in Children.[6] For systolic pressure the mean (SD) was 0·72 (1·29) (median 0·77). For diastolic pressure the mean (SD) was 0·48 (1·14) (median 0·54) (figs 1 and 2).

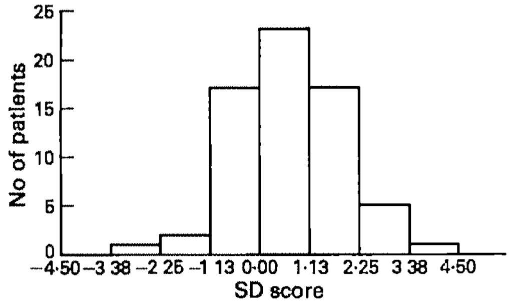

Figure 1 Frequency histogram: SD scores for systolic blood pressure.

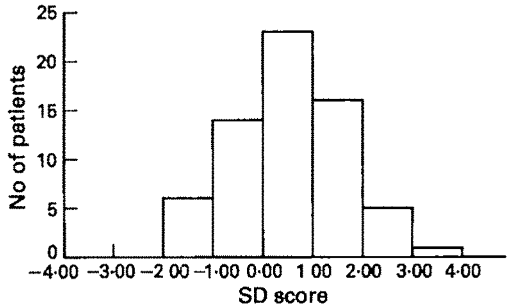

Figure 2 Frequency histogram: SD scores for diastolic blood pressure.

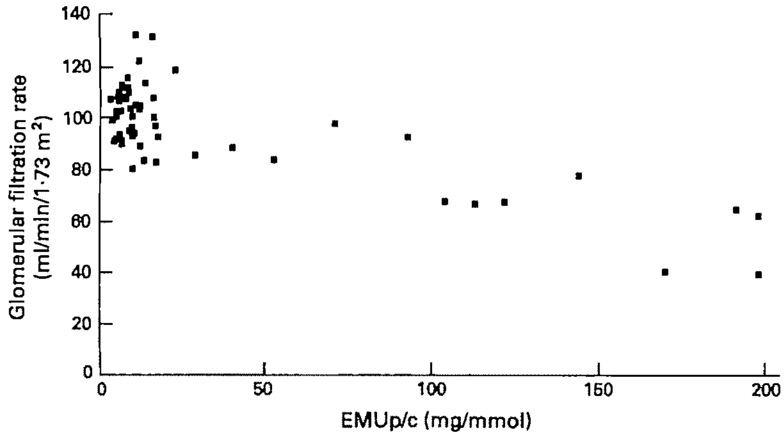

Figure 3 Correlation between glomerular filtration rate and the EMUp/c

URINARY TRACT INFECTIONS

Nine patients had recorded urinary tract infections. Five had a EMUp/c less than 20 mg/mmol and four had a EMUp/c greater than 20 mg/mmol. Only one of these patients had recurrent infections; all the others were single episodes that were successfully treated.

GLOMERULAR FILTRATION RATE

Results of glomerular filtration rate estimations were available from 55 patients. Only four of these were obtained from chromium-51 labelled EDTA clearance measurements; the rest were estimated from serum creatinine concentrations. Forty six patients had a EMUp/c less than 20 mg/mmol and nine greater than 20. No patient had a glomerular filtration rate less than 80 ml/min/1·73 m² in the group with a EMUp/c less than 20 mg/mmol, and their mean glomerular filtration rate was 104·51 ml/min/1·73 m² (96·01–132·35). In those patients with a EMUp/c greater than 20 mg/mmol, three (33%) had a glomerular filtration rate less than 80 ml/min/1·73 m²) (mean 88·66 (39–121·6)). The mean (range) intervals between nephrectomy and glomerular filtration rate results were 3·36 (0·1–11·02) years and 9·52 (1·6–22·2) years for those with a EMUp/c less than and greater than 20 mg/mmol respectively. There was a significant correlation between the EMUp/c and glomerular filtration rate (Pearson's correlation coefficient −0·61) (fig 3). The glomerular filtration rate of the five patients with bilateral tumours are shown in table 1.

CHARACTERISTICS OF PATIENTS WITH A EMUP/C >20 MG/MMOL

Table 2 summarises the main features of those 11 patients with abnormal renal function. Their mean age at nephrectomy was 2·42 years. Compared with 3·59 years for the 64 patients with a EMUp/c less than 20 mg/mmol. This difference was not significant. Four of the patients were severely affected (EMUp/c >80 mg/mmol) and three of these had bilateral tumours. Of the seven patients with less severe proteinuria (EMUp/c 20·3–28·9 mg/mmol), only one had bilateral tumours. This patient's values

Table 1 Glomerular filtration rate for children with bilateral Wilms' tumour

Patient No	Glomerular filtration rate (ml/min/1 73 m²)	EMUp/c (mg/mmol)
1	39·0	>20
2	61·7	>20
3	97·2	>20
4	116 5	>20
5	115 5	<20

Table 2 Characteristics of children with a EMUp/c greater than 20 mg/mmol

Patient No	*Site of tumour*	*Operation performed**	*Chemotherapy†*	*Radiotherapy*	*Other characteristics*	*Age at nephrectomy (years)*	*No of urinary tract infections*	*Interval between nephrectomy and measurement (years)*	*EMUp/c (mg/mmol)*
1	Bilateral	CU	VAC	Renal bed	Polycystic	1·1	1	22	198
2	Bilateral	BPN	AVA	—	—	2·0	1	5	42
3	Bilateral	BPN	AVA	—	Polycystic aniridia, Wilms' pyelonephritis	1·7	Recurrent	12	170
4	Bilateral	UN	AVA VICA	Whole lung	—	2·4	1	3	43
5	Unilateral	UN	AVA VIC	Renal bed, pelvis	—	1·9	—	13	40
6	Unilateral	UN	VCR	Whole abdomen	—	3·4	—	14	27
7	Unilateral	UN	AVA VI	Whole abdomen, pelvis	—	7·0	—	5	93
8	Unilateral	UN	AV	—	Dysmorphic syndrome	2·7	—	5	29
9	Unilateral	UN	AVA	—	—	1·7	—	16	56
10	Unilateral	UN	AVA	—	Toxic gentamicin concentrations	1·5	—	15	22
11	Unilateral	UN	AV	Whole abdomen	—	0·8	—	16	23

*UN=unilateral nephrectomy; BFN=bilateral partial nephrectomy; CU=complete nephrectomy and contralateral partial nephrectomy
†VAC=vincristine, actinomycin, and cyclophosphamide, AVA=actinomycin, vincristine, and Adriamycin, VICA=vincristine, ifosfamide, and carboplatin, VIC=vincristine, ifosfamide, and cisplatin, VI=vincristine and ifosfamide, AV=actinomycin and vincristine; VCR=vincristine.

for the EMUp/c have steadily decreased from 52 to 20·3 mg/mmol.

There were four patients with bilateral tumours necessitating extensive surgery. One of these patients had unilateral multicystic renal dysplasia and the other had bilateral multicystic renal dysplasia and the aniridia–Wilms' tumour syndrome, recurrent urinary tract infections, and histological evidence of chronic pyelonephritis. The other patient's renal biopsy sample showed widespread interstitial fibrosis, tubular atrophy, marked glomerular enlargement, and hilar arteriolar thickening with intramural hyaline deposits. Two of 11 glomeruli were globally sclerosed, with no focal segmental sclerosis being identified. These findings probably represented the results of previous irradiation with changes of glomerular hyperfiltration superimposed. The biopsy samples had been taken in view of the severity of these patient's renal disease. Another of these four patients also received ifosfamide (10·8 g/m^2), carboplatin (733·3 mg/m^2), and whole lung irradiation for pulmonary relapses. Only one patient in this group received renal radiation (150 cGy). Of the remaining seven patients (unilateral tumours), two had Beckwith's syndrome. They received whole abdominal radiation (2250 and 3000 cGy), one of them also receiving ifosfamide (60 g/m^2) for a recurrence of the tumour. Another patient with a recurrence of the tumour received treatment that included ifosfamide (60 g/m^2) and cisplatin (300 mg/m^2). One patient received whole abdominal radiation, another received acyclovir for chickenpox prophlyaxis and toxic concentrations of gentamicin during treatment of fever and neutropenia. One patient had a familial syndrome of mental retardation and hypotonia. In the remaining patient no additional features were identified. A total of three patients has received nephrotoxic drugs, making it impossible to determine the correlation between drug dose and degree of proteinuria. None of the patients with normal protein excretion had received nephrotoxic drugs.

Discussion

One of the earliest studies of renal function in survivors of Wilms' tumour was carried out by Mitus *et al.*[7] It focused on the role of radiotherapy to the remaining kidney and calculated the dose of radiation using the known scatter of radiation from the old orthovoltage machines. They concluded that at doses greater than 1200 cGy there was significant kidney damage. Barrera *et al* found that only two of 16 children had mild proteinuria.[8] They had normal glomerular filtration rates, were normotensive, and radiotherapy was not found to be important in the aetiology of the proteinuria. Two studies have been published suggesting that renal function is normal for most survivors of unilateral Wilms' tumour. In the study by Bhisitkul *et al*,[9] renal functional reserve was found to be normal in 12 survivors of unilateral Wilms' tumour (follow up 9–23 years) and their matched controls. This was determined by measurement of creatinine clearance before and after an acute protein load by mouth. They concluded that for up to 15 years after nephrectomy for unilateral Wilms' tumour there was no evidence of hyperfiltration injury. In the study by Makipernaa *et al* four of 30 subjects had a subnormal kidney length and five had hypertension.[10] Tubular function was normal, and albumin excretion was greater than 20 mg/24 hours in three subjects. No correlation was established between albuminuria and treatment modalities. The follow up time for this study was 11–28 years. There have, however, been case reports of children with congenital single kidneys who have subsequently developed serious renal impairment. Thorner *et al* reported three children with single kidneys who developed persistent proteinuria and deterioration in the glomerular filtration rate.[11] All had renal biopsy samples showing focal segmental glomerulosclerosis. In another report two children treated for Wilms' tumour at 3·5 and 18 months of age developed persistent proteinuria and glomerulosclerosis,[12] one of them requiring a kidney transplant at 21 years of age.

In our study we used the protein/creatinine index in early morning urine samples as an indicator of renal function, and only carried out more detailed assessment in those patients with abnormal results. Support for this approach can be found in animal and human studies. Provoost *et al* carried out work on rats in which they assessed the effect of various levels of dietary protein on renal function in nephrectomised and non-nephrectomised rats.[13] Examination of their curves for glomerular filtration rate and urinary protein excretion shows that proteinuria preceded the decrease in glomerular filtration rate. A similar approach was taken by Milford *et al.*[14] In their study of children with diarrhoea associated haemolytic uraemic syndrome, they found a strong correlation between the level of protein excretion and renal function. Barratt *et al* also observed that significant glomerular disease could be present in the absence of any changes in glomerular filtration rate measurements.[15] The measurement of proteinuria therefore provides a method of detecting glomerular disease at an early stage and a way of monitoring its course and response to treatment. Assessment of proteinuria can be carried out simply and reliably by measurement of the protein:creatinine ratio in single urine samples,[16,17] the effect of exercise and the upright posture being eliminated by using early morning urine.[4]

The results of our study show that 10 of 11 of the patients with an abnormal EMUp/c had adverse factors in addition to nephrectomy contributing to impaired renal function. This finding is supported by another study of patients undergoing nephrectomy in childhood.[18] The significance of the syndrome of mental retardation, dysmorphism, and hypotonia in relation to renal function remains unclear, however. The presence of bilateral tumours was clearly associated with the subsequent development of proteinuria (four of five such patients), the common feature being a loss of large proportions of kidney tissue. The most severely affected patients were those with bilateral tumours (three of four), the less severely affected having unilateral tumours (six of seven). In addition to this two of the severely affected patients had underlying renal abnormalities that could themselves have led to endstage renal failure (multicystic dysplastic kidneys), and one subsequently received ifosfamide and carboplatin (nephrotoxic drugs). Although we have no biopsy material, it is well known that Beckwith's syndrome is associated with renal disease.[19] The two patients with this syndrome had received whole abdominal radiation and one had also received ifosfamide, so they had multiple reasons for the development of impaired renal function.

The one patient with no obvious factors in addition to nephrectomy could have impaired renal function due to glomerular hyperfiltration. This has been described in several studies on unilaterally nephrectomised rats[1,2,20] and the underlying pathology is identified as focal segmental glomerulosclerosis. Other studies have shown glomerular hyperfiltration in children and young adults with diabetes mellitus.[21–23] Morita *et al*,[24] in their study of renal biopsy samples from children and adults with reflux nephropathy, found a strong positive correlation between the percentage of glomeruli showing focal segmental glomerulosclerosis and the severity of proteinuria ($r=0{\cdot}89$; $p<0{\cdot}0001$). The two renal biopsy samples showed chronic pyelonephritis in one and early changes of glomerular hyperfiltration in the other.

Our study found that most (86%) of the children surviving Wilms' tumour had a normal renal function. Impaired renal function was found in 10% of patients with a unilateral Wilms' tumour (seven of 71), and 80% with bilateral tumours (four of five). Bilateral tumours clearly pose a high risk of developing impaired renal function. Pre-existing renal abnormality, whole abdominal radiation, and the use of nephrotoxic drugs provided extra risk factors for those patients with unilateral and those with bilateral tumours. The age at nephrectomy was lower for patients with reduced renal function compared with those whose renal function was normal, though this difference was not statistically significant. Other studies have also found similar results.[25,26] We consider that the use of the protein/creatinine index in early morning urine samples, with measurement of blood pressure, is a simple way of monitoring these patients. Our current practice is to perform a baseline determination of the EMUp/c on completion of treatment and annually thereafter as long as results are normal. When abnormal results are obtained the patients are referred to the nephrology department for further evaluation and management.

To understand more clearly the natural course of renal function after nephrectomy for Wilms' tumour longitudinal studies over prolonged periods of time are needed. It is planned to carry out such studies in our centre, and these will include measurements of blood pressure, renal mass, and function, and storage of urine samples should allow future measurement of proteins not currently measurable.

This study was supported by the Leukaemia Research Fund We also thank Dr F Raafat (Department of pathology, Birmingham Children's Hospital) and Professor R H R White (Department of nephrology, Birmingham Children's Hospital) for allowing us to quote their opinions on the renal biopsy samples, and Dr C M Taylor (department of nephrology) for his advice on the preparation of this paper

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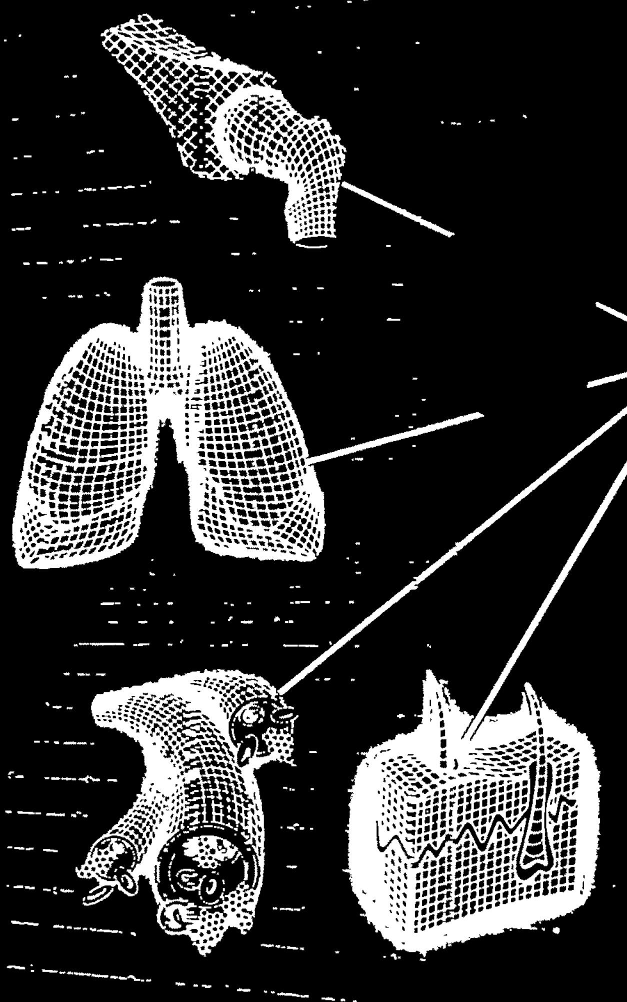

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Teachers' perceptions of epilepsy

M J Bannon, C Wildig, P W Jones

Abstract

A questionnaire survey undertaken among 142 schoolteachers in North Staffordshire revealed most of the respondents did not feel confident when teaching children who had epilepsy and a minority considered their knowledge of the subject to be adequate. Only four teachers had received recent specific instruction on childhood epilepsy and the majority requested training on epilepsy and other medical conditions. Despite this lack of confidence and specific training, the respondents demonstrated good general knowledge of epilepsy and adequate awareness of the difficulties encountered by epileptic schoolchildren. If optimal care is to be achieved for children with epilepsy, then teachers must feel confident with this subject. School health services have a clear role in ensuring that teachers have sufficient knowledge of childhood epilepsy, that they have adequate support, and that communication between teachers, parents, and paediatricians is encouraged.

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Teachers, in general, do not receive any formal instruction on childhood illness during their training. Following the integration of children with special needs into mainstream schools, teachers are now quite likely to encounter children with a wide variety of significant medical disorders. Previous studies have already demonstrated a lack of knowledge among school teachers of common chronic disorders such as asthma[1] and diabetes.[2] Epilepsy is one of the more common diseases encountered among schoolchildren with an overall prevalence of four to five per thousand.[3]

A survey in 1975 demonstrated that teachers had a limited understanding of epilepsy and that little or no support on the subject was available to them from the school medical service.[4] It is important to consider the attitudes and awareness that teachers may have regarding childhood epilepsy. Although a common disorder, it still possesses a social stigma that may result in parental reluctance to share information with teaching staff. In addition, there is evidence to suggest that children with epilepsy, as a group, are more prone to learning disorders.[5] As much as 40% of a child's waking life is spent at school, and during that time teachers could have an important part to play in the management and surveillance of children with epilepsy.

The aim of this study was to determine current attitudes and awareness of childhood epilepsy held by school teachers in North Staffordshire.

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Methods

One hundred and forty nine schoolteachers in 12 mainstream schools were invited to participate in the study. Teachers' knowledge and attitudes were determined by means of a self completed questionnaire consisting of 39 questions. The questions were mainly of the true/false variety but also allowed for teachers to express their opinions by means of free text. The areas covered by the questionnaire included:

(1) Teachers' personal details incuding age, sex, years of teaching experience, and whether they had first aid training.

(2) General knowledge of the aetiology, presentation, treatment, and outcome of schoolchildren with epilepsy.

(3) Previous experience of epilepsy in children, including personal encounters with epileptic children and previous specific training on childhood epilepsy.

(4) Views regarding possible learning difficulties in epileptic children and the most appropriate school placement for them.

(5) Appropriate restrictions of activity for children who had epilepsy; appropriate careers for them and views regarding the difficulties that might be encountered by them on leaving school.

(6) First aid treatment of epileptic fits and views regarding the administration of rectal diazepam at school.

(7) Overall confidence of the teachers when presented with a child with epilepsy.

(8) Levels of communication between parents, teachers, and medical staff.

Statistical analysis of results was achieved by means of the Number Cruncher Statistical System statistical package version 5 (Utah, 1989). Because of occasional missing data, totals in the tables may not add up to 100%.

Results

(1) TEACHERS

One hundred and forty two teachers (44 male, 98 female) participated in the study; seven teachers refused. Ninety four teachers (66%) were aged 35 years or more and 90 respondents (63%) had 10 or more years of teaching experience. Twenty seven teachers (19%) were first aiders.

(2) GENERAL KNOWLEDGE OF EPILEPSY

Table 1 summarises the responses to 10 general

Table 1 Teachers' general knowledge of epilepsy. Figures are number (%) of teachers

	Correct answer	Actual answers		
		True	*False*	*Don't know*
1. An epileptic fit happens when there is a discharge of abnormal electrical activity in the brain	True	109 (77)	5 (4)	28 (20)
2 All children who have fits have epilepsy	False	129 (91)	3 (2)	10 (7)
3. Epilepsy can run in families	True	94 (66)	13 (9)	35 (25)
4 In some epileptic children a fit can be triggered by flashing lights	True	123 (87)	6 (4)	13 (9)
5. Children with epilepsy are usually educationally subnormal	False	0 (0)	114 (99)	2 (1)
6. Drugs used to treat epilepsy can cause drowsiness	True	85 (60)	8 (6)	49 (34)
7 The outlook for children with epilepsy is mostly good	True	119 (84)	2 (1)	21 (15)
8. The proportion of schoolchildren with epilepsy is approximately 0·5–1·0%	True	38 (27)	42 (30)	62 (44)
9 Epilepsy can occur following a head injury	True	65 (46)	18 (13)	59 (41)
10 The test most often used to diagnose epilepsy is called an EEG	True	89 (63)	6 (4)	47 (33)

knowledge questions concerning epilepsy. The number of correct responses varied from 99% to question 5, which asked if children with epilepsy were usually educationally subnormal, to 27% correct for question 8, which asked the prevalence of epilepsy in schoolchildren. The mean overall number of correct replies was 70%.

Table 2 Teachers' previous experience of epilepsy. Figures are number (%) of teachers

	Responses		
	Yes	*No*	*Don't know*
Have you ever witnessed a fit?	97 (69)	43 (31)	1 (1)
Have you ever taught a child with epilepsy?	81 (57)	53 (38)	7 (5)
Have you a friend or relative with epilepsy?	41 (29)	93 (66)	7 (5)
Have you attended courses on epilepsy?	4 (3)	137 (97)	0 (0)
Have you read leaflets on epilepsy?	31 (22)	108 (77)	2 (1)

Table 3 Responses of teachers to questions regarding epilepsy and learning. Figures are number (%) of teachers

	True	*False*	*Don't know*
Children with epilepsy are more likely to have problems with learning	21 (15)	97 (68)	24 (17)
	Yes	*No*	*Don't know*
Would you accept a lower standard of work from a child with epilepsy?:	7 (5)	118 (83)	18 (12)
Where should children with epilepsy be educated?			
All in normal schools	68 (48)		
Most in normal schools	65 (46)		
Some in special schools	6 (4)		
Most in special schools	0 (0)		
Don't know	2 (1)		

(3) PREVIOUS EXPERIENCE OF EPILEPSY (TABLE 2)
The majority of teachers had witnessed an epileptic fit (n=97; 69%) or had taught a child with epilepsy (n=81; 57%). Forty one teachers (29%) had either a friend or a relative with epilepsy. Thirty one teachers (22%) could remember reading leaflets or other literature concerning epilepsy and four teachers (3%) had attended a seminar or course on childhood epilepsy within the last five years. When asked from whom they would obtain further information regarding epilepsy, 120 (88%) would approach the school doctor; 12 (8%) would make inquiries from the child's general practitioner, and five (4%) would ask the school nurse.

(4) EDUCATIONAL ASPECTS OF EPILEPSY
Ninety seven teachers (68%) did not consider that children with epilepsy were more likely to have problems with learning and their consensus of opinion was such that they should not expect a lower standard of work from children with epilepsy (table 3). The majority of teachers were of the opinion that either all or most epileptic children should be educated in mainstream schools.

(5) RESTRICTIONS
Table 4 refers to the teachers' responses concerning restrictions that might be imposed on schoolchildren with epilepsy. In general, teachers considered football, running, and gymnastics but not rock climbing to be appropriate sports. They disagreed with statements that children with epilepsy should never ride a

Table 4 Responses of teacher to questions regarding childhood epilepsy and restrictions. Figures are number (%) of teachers

	True	*False*	*Don't know*
1 The following are suitable sports for *most* children with epilepsy:			
Football	120 (85)	2 (1)	20 (14)
Running	121 (85)	2 (1)	19 (14)
Rock climbing	23 (16)	82 (58)	37 (26)
Gymnastics	71 (50)	31 (22)	40 (28)
2 Children with epilepsy must never ride a bicycle	3 (2)	116 (82)	23 (16)
3 Children with epilepsy will never be allowed to drive	12 (9)	102 (72)	28 (19)
4 Children with epilepsy should not participate in laboratory experiments	1 (1)	117 (83)	24 (17)
5 Children with epilepsy must never go swimming	7 (5)	121 (85)	14 (10)
5. Suitable careers for children with epilepsy are:			
Teacher	97 (68)	18 (13)	59 (19)
Bus driver	10 (7)	111 (78)	21 (15)
Nurse	77 (54)	31 (22)	34 (24)
Accountant	127 (89)	0 (0)	15 (11)

bicycle, never be allowed to drive, never participate in laboratory experiments, and never go swimming. Suitable careers, in their opinion, for epileptics were teaching, nursing, accountancy, but not bus driving. The teachers were asked to state those difficulties which children with epilepsy might encounter when leaving school and their responses were as follows: employer discrimination (n=59; 42%), ignorance of others (n=29; 20%), problems of social integration (n=27; 19%), lack of acceptance by colleagues (n=12; 8%), and limited job choice (n=11; 7%).

(6) TREATMENT OF EPILEPTIC FITS

Table 5 indicates the answers to a question where teachers were asked to define their responses in the event of a child having an unexpected fit in the classroom. The majority of teachers would place the child in the recovery position, would not place a handkerchief in the child's mouth, would not immediately call for an ambulance, and would not attempt to restrain jerking limb movements. As to the appropriateness of always sending a child home after a fit, there was some uncertainty regarding this with almost equal numbers answering 'yes' or 'don't know'. Teachers were also asked who was the most appropriate person to administer rectal diazepam. Fifty teachers (35%) declined to answer this question. Of those who responded the answers were as follows: teacher (n=7; 8%), head teacher (n=2; 2%), school nurse (n=39; 42%), doctor (n=23; 25%), classroom assistant (n=3; 3%), and first aider (n=17; 18%). The teachers were also asked to give reasons for their answers to this question and comments included that they would not accept responsibility for this treatment and that training in the administration of rectal diazepam would be needed.

(7) LEVELS OF CONFIDENCE

The respondents were asked if they could evaluate their overall levels of confidence when teaching or supervising epileptic children. Only seven teachers (5%) felt very confident when dealing with children who had epilepsy, 44 (31%) felt quite confident, and 90 (64%) replied that they did not feel confident. Teachers who had previously witnessed an epileptic fit had significantly higher levels of confidence than those who had not ($\chi^2_1=18\cdot65$, $p<0\cdot001$). Similarly, confidence was higher in those who had a friend or relative who had epilepsy ($\chi^2_1=11\cdot20$, $p<0\cdot001$). Five teachers (4%) felt that they knew enough about childhood epilepsy, 120 (87%) considered their knowledge inadequate, and the remaining 12 (9%) were not sure. Sixty six teachers (46%) state that their confidence would be increased by further training in childhood epilepsy and 63 (44%) required more information in the form of booklets and leaflets. The majority (n=129; 92%) felt that further instruction in childhood epilepsy would be of benefit and also requested instruction in asthma, diabetes, haemophilia, cystic fibrosis, hearing impairment, and AIDS.

Table 5 Teachers' management of an epileptic fit Figures are number (%) of teachers

If a child suddenly had a fit in your classroom would you·	*Yes*	*No*	*Don't know*
1. Immediately call for an ambulance	12 (9)	106 (75)	24 (16)
2 Place child in the recovery position	121 (85)	7 (5)	14 (10)
3. Place a handkerchief in the child's mouth	15 (11)	87 (62)	40 (27)
4. Restrain jerking limb movements	7 (5)	107 (75)	28 (20)
5. Send child home after he had recovered	41 (29)	53 (47)	48 (34)

(8) COMMUNICATION BETWEEN TEACHERS, PARENTS, AND THE SCHOOL MEDICAL SERVICE

Of the 81 teachers who to their knowledge had taught a child with epilepsy, 40 (49%) were first made aware of the child's epilepsy by prior discussion with parents, 24 (30%) first learned of the child's epilepsy when the child had a fit in school, and 11 (14%) teachers had discussion with either the school nurse or doctor. In general, teachers welcomed the notion of prior discussion with an epileptic child's parents and they considered the following topics to be of use in this context: frequency of fits, medication, warning signs of imminent fits, and parent contact details.

Discussion

This survey has revealed many positive findings regarding teachers' perceptions of childhood epilepsy. In particular, the teachers are to be commended on their depth of general knowledge of childhood epilepsy in spite of their lack of previous training on the subject. It would appear from this study that this knowledge was acquired as a result of personal experience over the years rather than from structured training. The teachers studied were relatively mature and experienced and this may have had a bearing on their responses to the general knowledge questions. It is interesting that their level of knowledge of childhood epilepsy was better than that of teachers in other studies when knowledge and attitudes to asthma[1] and diabetes[2] were studied.

The positive attitude demonstrated by the teachers regarding educational aspects of children with epilepsy is very encouraging and is in contrast to attitudes found in earlier studies.[6 7] Perhaps their views, if anything, are somewhat optimistic in some respects. The teachers in this study, in general, did not consider that epileptic children were more prone to learning difficulties. The subject of academic outcome in these children is controversial but many studies, including that by Stores and Hart,[8] have indicated that children with epilepsy, in general, are more likely to have learning difficulties. The reasons for this are unclear at present but teachers should at least be aware of the potential for academic failure in epileptic children so that their progress in school can be closely monitored. It is of interest that most teachers considered a career in teaching to be appropriate for a school leaver who had epilepsy. This again emphasises the positive attitude of the teachers. Current recommendations, however, require that teacher training applicants must be free from seizures for three years and that, while in post, they may be barred from teaching physical education, craft, science, and home economics.[9] The final encouraging outcome from this study is the request made by the teachers for further training or instruction in epilepsy and other common childhood disorders.

The main finding from this study was the overall lack of confidence among the teachers despite possessing both reasonable knowledge and considerable awarenes of the difficulties faced by epileptic schoolchildren. A number of factors may have combined together to contribute to undermining the confidence experienced by the teachers when they encounter children who have epilepsy. In the first instance, lack of structured training on epilepsy is likely to be relevant. A fear of the unknown, especially among younger teachers, and a lack of clarity of what is expected from them as professionals can result in anxiety based upon lack of experience and relevant knowledge. Secondly, lack of proper communication between parents, medical staff, and teachers will also result in uncertainty. It is regrettable that our findings are similar to those of Holdsworth and Whitmore who, in 1974, demonstrated similar lack of communication.[4] While knowledge and attitudes of teachers in this study have certainly improved since then, it would appear that levels of communication between all interested parties remain the same. A supreme example of lack of communications would be those 24 instances where teachers were first made aware of a child's epilepsy by the child having a fit in school.

The subject of administration of rectal diazepam by teachers in mainstream schools is fraught with difficulty. There is no doubt that in certain circumstances rectal diazepam can be an extremely effective method of treatment,[10] especially in status epilepticus. However, training and support is needed if teachers are to use this drug effectively and it could be argued, quite reasonably, that its use might be better restricted to special schools where pupil supervision is greater and help from a classroom assistant is available. There is a considerable body of teacher opinion opposing the administration of rectal diazepam by teachers in mainstream schools for this reason.[11]

THE WAY FORWARD

(1) Training

Several writers have called for the institution of instruction on common medical disorders while teachers are in training.[1 4] While this recommendation is perhaps relevant in concept, following recent changes in the training of teachers,[12] it is unlikely to be practical. Teachers will now spend less overall time in training and it seems unlikely that time will be set aside in order to increase their awareness of medically related issues. In this event, the onus for training of teachers in common childhood disorders must now lie with local health authorities. This should be undertaken by health authorities as a matter of some urgency especially for newly qualified teachers. An appropriate training package could be offered that would include aspects of medical illnesses in childhood which have particular relevance for schools.

(2) Communication

The importance of adequate communication between parents, teachers, and the school medical service cannot be overemphasised. It seems a pity that this aspect of the care of epileptic children has not greatly improved since the study by Holdsworth and Whitmore.[4] This lack of communication could be improved in several ways. Hospital paediatricians should have close liaison with colleagues in the school health service when treating schoolchildren with epilepsy. School nurses, in particular, are in a good position to ensure that adequate channels of communication exist between parents, school, and hospital services. The parent held child health record has already been shown to improve communication between parents and other parties and could be of great benefit here.[13] Community paediatricians, as part of their advocacy role, have an important coordinating function with regard to the integration of children with epilepsy into mainstream schools and could enlist the help of the voluntary sector, including the British Epilepsy Association, which has already produced helpful training material for teachers.

(3) Support

Once an epileptic child is admitted into school, ongoing support and advice could reasonably be provided by the school health team of school doctor and nurse. Now that most authorities have at last abandoned routine medical examinations for all school entrants, there should be more time available for this valuable work.

(4) Reduction of social stigma

There is no doubt that some of the difficulties faced by epileptic schoolchildren result from the social stigma that the illness attracts. Epilepsy remains a poorly understood and sometimes feared illness by the general public. Colver advocated a community based campaign to increase public awareness of asthma.[14] Perhaps the time has now come for a similar campaign to increase awareness of childhood epilepsy in order to reduce its ongoing stigma. Such a campaign would do much to facilitate the successful integration of children who have epilepsy into mainstream schools.

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Growth hormone deficiency during puberty reduces adult bone mineral density

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Abstract

Bone mineral density (BMD) was evaluated by dual energy *x* ray absorptiometry in 60 adults (33 males, 27 females; aged 50, range 23–76 years) who were growth hormone deficient from various causes for 10·4 (1–31) years. Adult patients who had acquired growth hormone deficiency before completion of puberty had significantly reduced mean (SEM) BMD compared with age matched healthy controls at the lumbar spine: 0·87 (0·09) *v* 1·20 (0·03) g/cm^2, femoral neck: 0·81 (0·06) *v* 1·08 (0·04) g/cm^2, and Ward's triangle: 0·68 (0·07) *v* 1·04 (0·05) g/cm^2. These values were also reduced compared with those of patients who had received human growth hormone during puberty. Untreated growth hormone deficiency when present during puberty results in reduced adult bone density.

(*Arch Dis Child* 1992;67:1472–4)

Little is known about the long term skeletal consequences of growth hormone deficiency other than reduced linear growth. Its importance for proper skeletal maturation has long been recognised as indicated by delayed bone age in growth hormone deficient children.[1] Lack of growth hormone during puberty when bone mineral density (BMD) is normally rapidly increasing[2 3] could result in severe osteopenia in adult life but this has not been specifically addressed in previous studies. We have investigated BMD in adults with growth hormone deficiency with special emphasis on those in whom pituitary deficiency was present before completion of puberty.

Clinical details of patients with growth hormone deficiency present during puberty

Patient No	*Sex*	*Diagnosis*	*Age at diagnosis (years)*	*Treatment*	*hGH treatment*
1	F	Craniopharyngioma	9	Surgery, cranial radiotherapy	Yes (2 years)
2	M	Craniopharyngioma	2	Surgery, cranial radiotherapy	Yes (6 years)
3	M	Craniopharyngioma	7	Surgery, cranial radiotherapy	Yes (7 years)
4	M	Craniopharyngioma	5	Surgery, cranial radiotherapy	Yes (11 years)
5	M	Craniopharyngioma	6	Surgery, cranial radiotherapy	Yes (1 year)
6	F	Astrocytoma	3	Cranial radiotherapy	No
7	M	Craniopharyngioma	16	Surgery, cranial radiotherapy	No
8	M	III ventricular tumour	15	Craniospinal radiotherapy	No
9	M	Suprasellar germinoma	13	Surgery, radiotherapy	No
10	F	Pituitary adenoma	15	Surgery	No

Subjects and methods

Sixty patients (33 males, 27 females; aged 50, range 23–76 years) were identified with severe growth hormone deficiency (peak growth hormone response below 5 mU/l after insulin induced hypoglycaemia) present for at least 12 months and absence of other conditions known to affect BMD. In 10 patients, growth hormone deficiency had been documented before completion of puberty (Tanner stage V). Clinical details of these patients and their treatments are shown in the table. Five patients had received human growth hormone (hGH) 0·25 IU/kg intramuscularly three times per week for 6 (2–11) years until fusion of the epiphyses. Mean duration of growth hormone deficiency in the 10 patients was 13·8 years (2–26) and all were adequately replaced with thyroxine, adrenal and sex steroids with no evidence of excessive replacement.

A control group of 17 healthy volunteers (12 males, five females) was also studied so that bone density in the patients with growth hormone deficiency before completion of puberty could be compared with that of a younger population matched for age, sex, weight, and height.

BMD expressed as g/cm^2 was measured by dual energy *x* ray absorptiometry (Lunar DPX) at lumbar vertebrae L2-L4 (referred to as lumbar spine), the femoral neck and at Ward's triangle, a region of the proximal femur consisting predominantly of trabecular bone. All scans were performed and analysed by the same operator. The coefficient of variation for BMD measurement at our institute is 1% at the lumbar spine and 2% at the femoral neck.

Comparisons of BMD between different groups of patients and controls were made by two tailed Student's *t* tests. Correlation coefficients were calculated from regression analysis and used to compare BMD at each site with all other clinical variables. Results are expressed as mean (range) or mean (SEM); $p<0·05$ was considered significant.

Results

The 10 patients who had been growth hormone deficient during puberty were younger than the 50 adult onset patients (30·4 (1·44) *v* 50·1 (1·95) years; $p<0·001$); they had been pituitary deficient for longer (14·9 (1·84) *v* 9·4 (1·01); $p=0·04$).

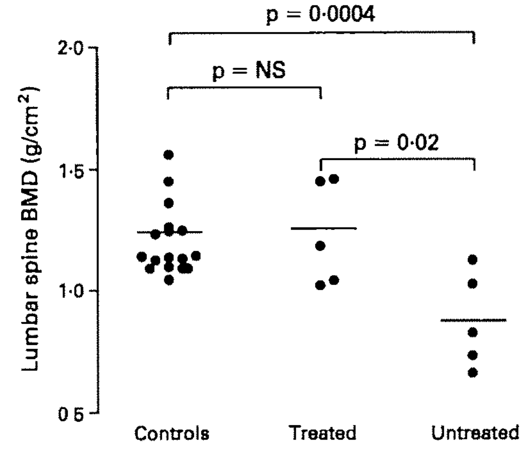

Figure 1 Lumbar spine BMD (g/cm^2) in adult patients with documented growth hormone deficiency during puberty who either were treated or were not treated with hGH compared with healthy controls matched for age, sex, weight, and height.

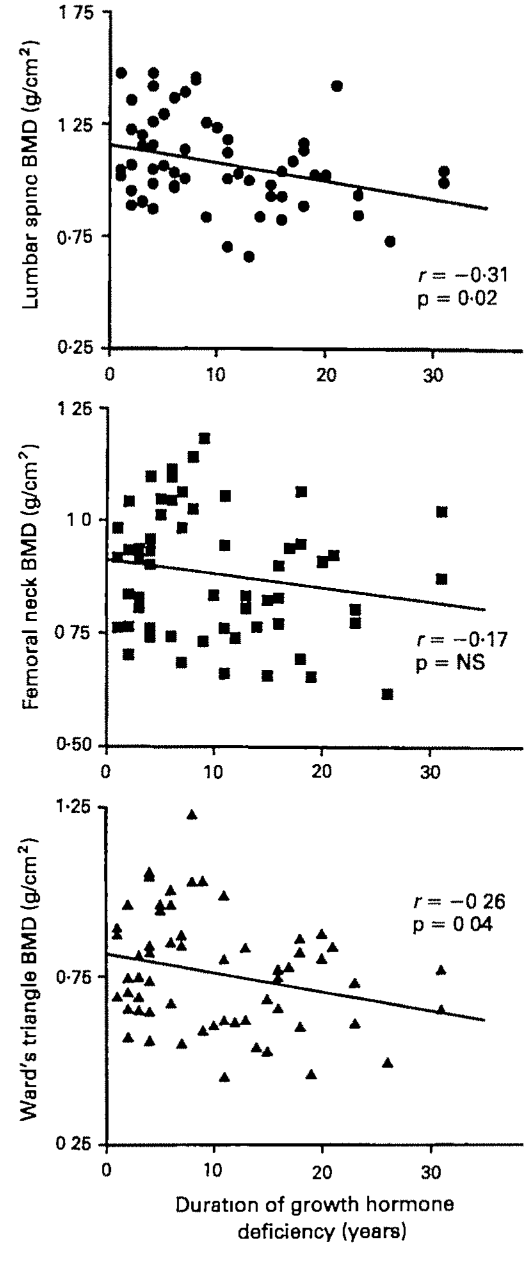

Figure 2 Relation of duration of growth hormone deficiency (years) and BMD at the lumbar spine, femoral neck, and Ward's triangle in 60 adults with growth hormone deficiency.

Growth hormone treated and growth hormone-untreated patients were similar with respect to the following variables: current age, sex, body mass index, onset and duration of growth hormone deficiency, duration of sex hormone deficiency and replacement. Patients who had not received replacement with hGH during puberty were shorter than those who had received hGH (158·6 (3·57) *v* 170·2 (2·65) cm; p=0·03). Mean (SEM) BMD (g/cm^2) in the five patients with pubertal deficiency not treated with hGH was appreciably reduced compared with normal controls at the lumbar spine: 0·87 (0·09) *v* 1·20 (0·03), p=0·0004; femoral neck: 0·81 (0·06) *v* 1·08 (0·04), p=0·004; and Ward's triangle: 0·68 (0·07) *v* 1·04 (0·05), p=0·002. Values were also reduced compared with those of growth hormone treated patients at the lumbar spine: 0·87 (0·09) *v* 1·23 (0·09), p=0·02; femoral neck: 0·81 (0·06) *v* 0·99 (0·05), p=0·05; and Ward's triangle: 0·68 (0·07) *v* 0·96 (0·08), p=0·03 (fig 1).

In adult onset growth hormone deficient patients, mean (SEM) BMD (g/cm^2) was: lumbar spine 1·08 (0·03), femoral neck 0·88 (0·02), and Ward's triangle 0·74 (0·02), which represented 89·9 (2·2)%, 96·1 (1·9)%, and 96·0 (2·7)% respectively of a normal reference population studied with an identical scanner (Lunar DPX Reference Manual, 1990). Values were similar in males and females.

A significant negative correlation was found between the duration of growth hormone deficiency and BMD measured at the lumbar spine (r=−0·31; p=0·02) or Ward's triangle (r=−0·26; p=0·04) but not at the femoral neck (fig 2).

Discussion

These results indicate that adult BMD is reduced in growth hormone deficient patients when present before completion of puberty and that, importantly, it can be normalised by hGH replacement during this period. This suggests that growth hormone has a pronounced effect on bone density during puberty at the time when peak bone mass is being attained.[3,4] This is consistent with previous reports of reduced radial and spinal bone mass in association with pubertal growth hormone deficiency.[1,5]

Additionally, growth hormone may be required for maintenance of peak bone mass as we noted a significant negative correlation between BMD and duration of adult onset growth hormone deficiency which was independent of other variables. We do not know if longer follow up in those patients who received hGH during puberty will reveal reduced BMD later in life.

Bone density measured by dual x ray absorptiometry as in this study may be influenced by the size of vertebral body.[6] It has been estimated that 50% of the pubertal increase in spine mineral is attributable to bone expansion rather than to an increase in BMD per unit volume.[7] As patients who had not received hGH during puberty were shorter than growth hormone treated patients, their lower BMD values could be, in part, related to their smaller vertebrae. However, this cannot be the whole explanation as BMD in these growth hormone untreated individuals was appreciably reduced compared with normal controls matched for height.

Our patients with pubertal pituitary deficiency had all been conventionally treated with gonadal steroids but some may have experienced a period of sex hormone deficiency before starting treatment. Even a brief period of hypogonadism may be associated with osteopenia.[8] The action of sex steroids in promoting the acquisition of bone mineral during puberty could require the presence of growth hormone to achieve their full effect.[7]

One patient who did not receive hGH during puberty had been treated with craniospinal irradiation and this could have contributed to his low bone density. Spinal growth during puberty has been shown to be impaired by spinal irradiation.[10] In such children, treatment with hGH may limit further reduction in height SD scores.[11]

If growth hormone is required for achievement of peak bone mass as suggested by this study, an anabolic rather than antiresorptive action is likely on the basis of in vitro[12 13] and in vivo[14 15] studies of growth hormone and insulin-like growth factor-I on bone metabolism. Interestingly, trabecular bone (lumbar spine, Ward's triangle) appears more sensitive to the effects of growth hormone than cortical bone. Osteoporosis associated with hypercortisolism or oestrogen deficiency also preferentially affects trabecular bone.[16 17]

Our results suggest that the long term consequences of growth hormone deficiency on BMD may be particularly serious in patients who develop pituitary deficiency before attaining peak bone mass. Growth hormone treatment should be considered in all such children to reduce the risk of osteoporosis in adult life.

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Hazards of parenteral treatment: do particles count?

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Abstract

After prolonged parenteral nutrition a 12 month old infant died with pulmonary hypertension and granulomatous pulmonary arteritis. A review of necropsy findings in 41 infants who had been fed parenterally showed that two of these also had pulmonary artery granulomata, while none of 32 control patients who died from sudden infant death syndrome had similar findings. Particulate contaminants have been implicated in the pathogenesis of such lesions and these were quantified in amino acid/dextrose solutions and fat emulsions using automated particle counting and optical microscope counting respectively. Parenteral feed infusions compounded for a 3000 g infant according to standard nutritional regimens were found to include approximately 37 000 particles between 2 and 100 µm in size in one day's feed, of which 80% were derived from the fat emulsion. In-line end filtration of intravenous infusions may reduce the risk of particle associated complications. A suitable particle filter is required for use with lipid.

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A 1000 g female infant born at 27 weeks' gestation developed necrotising enterocolitis after a period of respiratory distress and hypoglycaemia. Perforation of the terminal ileum led to laparotomy and formation of an ileostomy, which was closed five months later. Subsequently, an anastomotic stricture and adhesions caused small bowel obstruction requiring further surgery. Septicaemia, recurrent rotavirus infection, and protracted diarrhoea precluded full enteral feeding. She died suddenly and unexpectedly at 12 months of age, having been parenterally fed for much of her life. Striking features at postmortem examination were a granulomatous pulmonary arteritis with some of the arteries being occluded by fibrin, together with dilatation and hypertrophy of the right ventricle secondary to pulmonary hypertension.

Identical lesions in drug offenders are thought to be related to intravenous injection of magnesium trisilicate dust used as a lubricant in drugs intended for oral administration.[1 2] Granulomata have also been described in patients who have received large volumes of intravenous fluids,[3] and they can be reproduced experimentally in rabbits by injection of saline containing particulate matter.[4] The aims of this study were, therefore, to establish how often pulmonary granulomata could be found at postmortem examination in both patients who had and those who had not received parenteral nutrition, and to determine the number and size of particles in parenteral feeding solutions.

Subjects and methods

NECROPSY STUDY

Subjects

Postmortem material from all parenterally fed infants from a regional neonatal intensive care unit who had died between 1980 and 1989 were reviewed. Forty one such patients were identified, with a median (range) gestational age of 28 weeks (25–40) and weight 880 g (450–2820). The most common indication for parenteral nutrition was prematurity and failure to tolerate enteral feeding in association with respiratory distress requiring ventilatory support (n=38); indications in the three remaining patients were necrotising enterocolitis, ischaemic colitis, and ileal atresia. Parenteral nutrition was prescribed according to a standard protocol[5] with a fluid intake of 150 ml/kg. The median (range) duration of parenteral feeding was 14 days (1–46).

Controls

Necropsy findings in 32 infants who had died over the same period from sudden infant death syndrome (SIDS) were reviewed. None had received intravenous treatment of any sort.

Although not a double blind study, all postmortem examinations were performed by the same person (DIR). Tissue sections from each lobe of each lung were routinely examined for particulate matter, such as glass or cotton fibres, and for pulmonary vascular granulomata.

PARTICLE STUDY

Six amino acid/dextrose feeds (Vamin 9 glucose, Kabi Pharmacia; 250 ml in plastic bags) and eight 35 ml aliquots of lipid emulsion (Intralipid 10%, Kabi Pharmacia; in plastic syringes) were constituted according to a standard prescription for neonatal parenteral nutrition,[5] including addition of trace elements, micronutrients, and vitamins. Particles in the feeds were counted in glassware precleaned by washing in laboratory detergent (Decon 90), water, propan-2-ol trichlorotrifluoroethane, propan-2-ol, and finally water. All washing solutions (except the detergent) were terminally filtered through 0·2 µm rated filters fitted to pressurised dispensers.

AUTOMATED PARTICLE COUNTING

Approximately 100 ml samples of Vamin dextrose solution were run into precleaned bottles (which registered <20 particles >2 µm in size per 10 ml sample volume when filled with filtered water). Numbers of particles in the ranges 2–5 µm, 5–10 µm, 10–25 µm, 25–40 µm, and 40–100 µm were determined in 10 ml aliquots of these samples using a Hiac PC-320 automated particle counter with attached D2–60 automatic bottle sampler.

OPTICAL MICROSCOPE COUNTING

Samples of Intralipid 10% (35 ml) were filtered through precleaned 0·8 µm membranes contained in precleaned filter funnels. The membranes were dried, made transparent, and particles in the range 2–5 µm, 5–10 µm, 10–25 µm, 25–40 µm, and 40–100 µm were counted using a Vickers M17 optical microscope (so that lipid droplets were not counted).

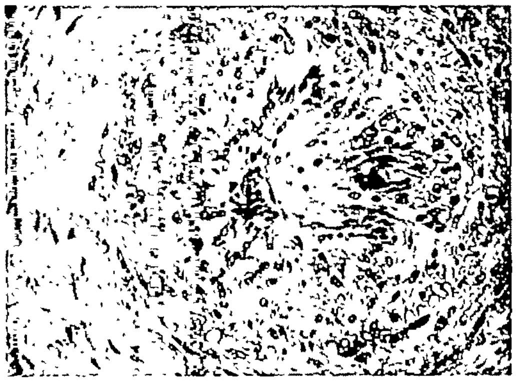
Results

NECROPSY STUDY

Postmortem examination of the 41 parenterally fed infants showed two cases of widespread pulmonary granulomata (figure), which had also been identified at the original necropsy. These were located throughout the pulmonary arterial system and showed characteristic features of intimal fibrosis associated with foreign body giant cells with or without associated thrombus formation. In most granulomata it was not possible to identify specific foreign material within the giant cells, but occasionally glass fragments and cotton fibres were easily visible under polarised light. No granulomata or foreign bodies could be found in those patients who died from SIDS.

PARTICLE STUDY

Particle counts recorded are shown in the table. In one day's parenteral feeding for a 3000 g infant, there were approximately 37 000 particles between 2 and 100 µm, with the majority (70%) being less than 5 µm size and only 4% being above 25 µm.



Section of neonatal lung showing granuloma with giant cells in the wall of a pulmonary artery. (Haematoxylin and eosin×300)

Discussion

Our findings confirm that pulmonary granulomata can be found in a small proportion of patients who have received parenteral fluids. Such granulomata formation has been convincingly related to both particulate contamination of intravenous solutions[3 4 6] and the development of severe cardiovascular disease,[1 2] and has been described in infants[7] as well as adults. We estimate that our index patient with pulmonary hypertension and right heart failure would have received approximately 5 million particles between 2 and 100 µm in size from parenteral feed solutions alone.

Early studies of intravenous fluids showed that components of rubber bungs, glass from bottles, and fungal spores were common particulate contaminants together with more exotic finds such as fragments of crustacean.[3] More recently the hazards of glass fragments[8] and cotton fibres from alcohol impregnated swabs have been highlighted.[9] Many particles appear to be organic in nature[10] and generated by chemical interactions when mixing solutions. Some undoubtedly come from within plastic infusion systems, arising during the process of manufacture. Although there are accepted standards for particle counts in large and small volume parenterals, no such standards exist for infusion systems.

As pulmonary capillaries vary between 8 and 12 µm in size, any particle larger than this is likely to be filtered out and retained in the pulmonary vascular bed. Animal experiments with intravenous injection of microspheres indicate that small particles enter the systemic circulation and end up in organs including liver and spleen.[11] The clinical significance of particles too small to be retained in the lungs is uncertain, although some haemodialysis patients have developed abnormal liver function thought to be a result of silicone particles in the liver derived from siliconised peristaltic blood pumps.[12]

Particulate contamination is known to cause phlebitis in peripheral vessels, a complication significantly reduced by filtration.[13] Perhaps such physicochemical interaction between particles and vessel walls involves very small as well as large particles. Certainly it is not simply particles large enough to get trapped in vessel lumens that trigger granulomata formulation, as often it is impossible to see any foreign body within the granulomata, while when glass

Mean (SD) particle count (by size) per 10 ml of amino acid/dextrose solution and per 35 ml of Intralipid 10%, with additives compounded according to standard regimen for infant <10 kg. and dispensed from plastic bags and plastic syringes respectively

Feed	*No of samples*	*Partical size (µm)*				
		2–5	*5–10*	*10–25*	*25–40*	*40–100*
Amino acid/dextrose	6	151 (24)	44 (13)	13 (5)	4 (3)	2 (2)
Lipid emulsion	8	5881 (1538)	766 (317)	729 (406)	418 (193)	28 (10)

particles can be identified they may be smaller than the vessel lumen itself. There is increasing evidence that interaction between particles and damaged endothelium may be implicated in microcirculatory disturbance which appears to be a key feature of adult respiratory distress syndrome and multiple organ failure in adult intensive care patients.[14]

In-line filtration of amino acid/dextrose mixtures is commonly performed using a 0·2 μm rated filter. This type of filter has been developed to retain any microbiological organisms contaminating feeds,[15] but its usefulness has been questioned[16] perhaps without consideration of its additional role as particle filter. Any hazards of particulate matter are more likely to occur in patients on long term intravenous treatment. Small infants who have a high fluid intake relative to their weight might be at particular risk. Since Intralipid droplets are similar in size to natural chylomicrons (0·6–1·6 μm) and also highly charged they cannot be filtered through a 0·2 μm membrane. This means that in our patients, even when the amino acid/dextrose mixture is filtered, four fifths of the particle load within the day's parenteral nutrition fluids is not retained.

Although we have focused attention on parenteral nutrition fluids, it has been estimated that the majority of particles delivered to a patient come from medications together with infusion solutions, ampoules, injection sites, and syringes.[17] Whereas in-line filtration of parenteral nutrition fluids seems desirable in patients on long term parenteral nutrition, any attempt to reduce the particle load delivered must take account of these other sources.

Increasing recognition that particulate contaminants may cause serious disease provides a persuasive argument for in-line end filtration of all intravenous fluids and injections given to patients needing intensive care. Such a policy could be cost effective through reducing phlebitis associated with peripheral infusions[13] or in prolonging intravenous administration set life.[18 19] Alternatives to glass ampoules[20] have already been developed and are associated with fewer particles than glass ampoules. The use of hypodermic needles with in-built 5 μm filters for drawing up solutions effectively removes many of the glass fragments seen with glass ampoules.

While the precise risks associated with particulate contaminants of intravenous treatment remain uncertain, it is clear that particles themselves are unwanted and unnecessary. There is mounting evidence that they may cause serious disease, particularly in sick patients. Standards for manufacture of administration systems are urgently required. As the manufacturing of small and large volume parenteral nutrition solutions is likely to remain associated with at least some level of particulate contamination, effective filtration will be the only way of preventing adverse clinical consequences. Future developments should include filters suitable for use with lipid emulsions.

We would like to thank Miss J Patterson for invaluable secretarial assistance

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Sinusitis-induced subdural empyema

Ruth Skelton, Wirginia Maixner, David Isaacs

Abstract

Over a 17 year period, 1975–91, 10 children were managed who had sinusitis-induced subdural or extradural empyema. Their ages ranged from 6 to 14 years, with a mean of 11 years. All presented with worsening headaches, fever, vomiting, all had neurological abnormalities, and all had symptoms or signs suggestive of sinusitis. Initial computed tomography gave normal results in five cases and the empyema was diagnosed on the second or third scan. All patients had symptoms for at least one to two weeks before the diagnosis was made. *Streptococcus milleri* was the organism most frequently implicated. Medical treatment was started in all cases on admission, but all required surgical intervention before resolution.

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Subdural or extradural pyogenic collections most commonly arise by direct extension of infection from meningitis or the sinuses. Subdural empyema secondary to bacterial meningitis tends to occur in small infants,[1] and is usually recognised clinically, readily diagnosed by computed tomography, and managed relatively early. Subdural or extradural empyema secondary to sinusitis, so called 'sinusitis-induced' empyema,[2] occurs in older children and is responsible for 50–70% of all subdural empyemas.[1 3] The clinical presentation of sinusitis-induced empyema is less well recognised and the diagnosis often delayed. Recent series of subdural empyema associated with sinusitis describe it as an illness predominantly of adolescent and young men, characterised by the rapid development of stupor, nuchal rigidity, seizures, and hemiparesis.[2 4] However the onset may be much more variable and often masked by prior antibiotic treatment.[3]

Table 1 Presenting characteristics of children with sinusitis induced subdural and extradural empyema

Patient No	*Age (years)*	*Sex*	*Duration of symptoms to presentation (days)**	*Total duration to diagnosis (days)†*	*No of scans to diagnosis*	*No of days from 1st to final scan*
1	10	M	10	17	3	3
2	12	M	5	8	1	
3	9	M	1	17	2	10
4	13	M	7	9	1‡	
5	7	M	6	25	2	21
6	12	F	14	14	1	
7	13	F	5	9	2	3
8	6	F	12	12	1‡	
9	14	M	1	12	1	
10	14	M	14	18	2	4

*Duration of symptoms up to presenatation at first hospital (local or teaching)
†Duration of symptoms from onset to diagnosis, that is *plus time in hospital before diagnosis made
‡Brain scan (before the availability of computed tomography).

We report a review of cases of subdural and extradural empyema associated with sinusitis seen at our hospital over a 17 year period 1975–91.

Methods

A search was made of the medical records of all children admitted to this hospital in the years 1975–91 inclusive, with a discharge diagnosis of subdural, extradural, or cranial empyema or abscess, sinusitis, or frontal osteomyelitis. A case was defined as having sinusitis-induced subdural or extradural empyema if there was radiological and/or operative evidence of a subdural or extradural purulent collection, and of sinusitis.

Results

Over the period 1975–91 a total of 10 children were found to have had sinusitis-induced subdural or extradural empyemas. Seven children had a subdural empyema, two had a extradural empyema, and one child had both.

PRESENTATION

The age range of the children with sinusitis-induced empyemas was 6 to 14 years (mean 11 years). Seven were over 9 years and seven were boys. Their symptoms, presentation, and findings are shown in tables 1 and 2. At admission, all 10 children complained of headache, nine had fever, eight had some neurological signs and the remaining two were lethargic. Two children were admitted 24 hours after sudden onset of fever, headache, seizures, and abnormal behaviour. Both also had periorbital swelling. They remained at a local hospital for a week, with an uncertain diagnosis. In both cases two weeks elapsed before the subdural empyema was diagnosed. Despite the initial speed of onset of symptoms, they did not progress over this time. One child had pustules that appeared over the forehead and another, with a bulging swelling of his forehead, had a true Pott's puffy tumour.

All 10 children had some symptoms or signs by admission, which could be attributed to acute bacterial sinusitis, but rarely recognised as such, that is tenderness or pain over the sinuses, purulent nasal discharge, or periorbital swelling. Only one child was diagnosed clinically as having sinusitis. She was admitted for treatment of this. In four children no mention of the sinuses was made on admission.

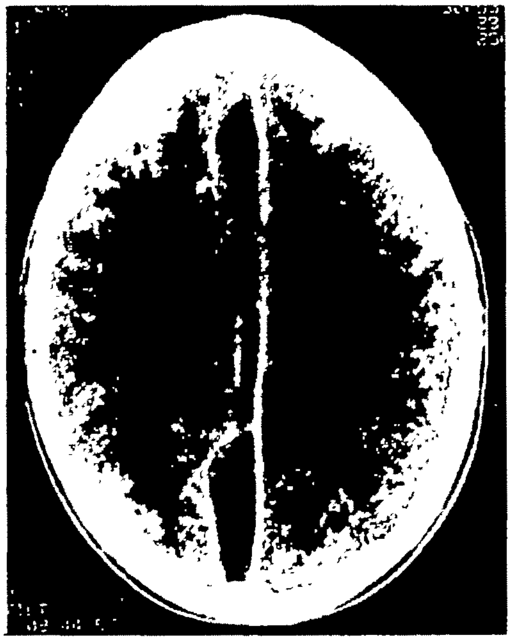
Table 2 Presenting clinical features of 10 children with sinusitis induced subdural or extradural empyema

Symptoms	*No of cases*
Headache	10
Fever	9
Vomiting	7
Seizures	6
Periorbital swelling	5
Lethargy	4
Irritability	3
Ptosis	3
Papilloedema	3
Hemiparesis	3
Neck stiffness	2
Tenderness over sinus	2
Rhinitis	2
VI nerve palsy	1

DIAGNOSIS

Plain radiographs or computed tomograms showed frontal, maxillary and/or ethmoid sinusitis in nine patients. In the last patient no radiography was performed but sinus infection was found at surgery. Three children had osteomyelitis, two of the frontal bones and one of the ethmoid. Seven of our 10 children had a lumbar puncture, including two with papilloedema. All had the typical picture associated with a subdural empyema,[3] of a mild pleocytosis, usually with 10–100×10^9/l white cells and sterile culture (see table 3). No patient had any side effects from the lumbar puncture.

There was always some delay in the diagnosis of empyema, which was made from eight to 25 days after the onset of symptoms. Patients experienced symptoms for up to 14 days before admission, and a further one to 19 days after admission, before the empyema was diagnosed. This delay occurred whether or not antibiotics were given. Five of the children had computed tomograms which did not show the empyema, before a definitive abnormal scan was obtained between three to 21 days later (see Figure). A minimum of eight days of symptoms occurred before the collection was picked up radiologically. After diagnosis surgery was usually carried out within a few days, although one child was medically treated for two weeks before surgery.



Computed tomogram of brain with sinusitis-induced subdural empyema. This shows an extensive collection of pus in the frontal subdural space, extending posteriorly along the flax.

ORGANISMS

In eight of our 10 patients, an organism was grown from the blood and/or the abscess, although all but one of the children had been receiving antibiotics before culture. *Streptococcus milleri* was the most common causative organism, being the sole organism grown in four of our patients. *Streptococcus mitis*, a group C streptococcus, bacteroides, and *Staphylococcus aureus* were each grown from blood or abscess in one patient. These organisms are similar to other studies[1 2 4] with streptococci being the most common organism present. Blood cultures were positive in four patients.

TREATMENT

All children were started on intravenous antibiotics on admission, often continuing for periods of one to two weeks before the empyema was diagnosed, usually a combination of penicillin, chloramphenicol, or a cephalosporin. All children had some form of surgery (table 3), and three required repeated procedures. Four children received two to three weeks of antibiotics before surgery. However none of the children improved before surgical drainage. Only two of the four children who had burr holes recovered with one operation. Of the six with craniotomy, only one required further intervention. Those who required multiple procedures were the patients who grew bacteroides and *S aureus*.

Table 3 Infectious characteristics of children with sinusitis induced subdural and extradural empyema

Patient No	*Organism*	*Site of empyema*	*Initial lumbar puncture (WCC×10^9/l*)*	*Treatment*	*Osteomyelitis site*	*Follow up*
1	Streptococcus C (blood culture)	Right subdural	0	Burr holes	—	Normal
2	No growth	Left frontal, subdural	25	Craniotomy	—	Normal
3	No growth	Left subdural	7	Craniotomy (multiple)	—	Hemiplegia, resolved three months, epilepsy, hydrocephalus
4	*S aureus* (abscess)	Left subdural/ extradural	9	Burr holes+ craniotomy	—	Normal
5	*S milleri* (sinus) *S mitis* (abscess)	Left extradural	63	Craniotomy	Ethmoid	Normal
6	*S milleri* (abscess)	Left subdural	—	Burr holes	—	Epilepsy
7	*S milleri* (blood culture, abscess)	Left extradural	—	Craniotomy	—	Hemiplegia and dysphasia, resolved six weeks
8	Bacteroides (abscess, blood culture)	Left subdural	28	Burr holes ×3	—	Normal
9	*S milleri* (abscess, blood culture)	Right subdural	9	Craniotomy	Frontal	Normal
10	*S milleri* (abscess)	Right subdural	—	Craniotomy	Frontal	Normal

*WCC=white cell count

OUTCOME

There were no deaths. Seven children had no residual neurological sequelae on discharge from hospital. Two children had persistent epilepsy, one of whom had hydrocephalus. Two children had hemiparesis, which resolved in six to 12 weeks (table 3).

Discussion

The age and sex distribution of our patients was similar to previous studies, confirming sinusitis-induced subdural empyema to be a condition mainly of adolescent children, with boys predominating over girls by about 3:1.

The severity of the presenting symptoms in our children varied, but they were quite consistent in their nature. Wald *et al* described the characteristic signs and symptoms of sinusitis-induced empyema by dividing them into four groups: those due to pansinusitis (mild headache, pyrexia), raised intracranial pressure (worsening headache intractable vomiting, deteriorating consciousness), meningeal irritation (neck stiffness), and focal neurological deficits.[5] She also suggested that extradural empyemas cause less cortical involvement and less impairment of consciousness than subdural empyemas.

The majority of our children had had symptoms for one to two weeks before presentation, initially those of simple sinusitis, that is fever, mild headache and malaise, although they were often not recognised as such, and usually treated non-specifically with oral antibiotics by the family doctor.

Symptoms usually progressed over the second week as signs of raised intracranial pressure developed, that is worsening headache, vomiting, seizures, and lethargy. Seizures, behavioural changes, and periorbital swelling usually precipitated hospital admission. Only two of our patients showed signs of meningeal irritation. Neurological signs were present in seven children. If lethargy and abnormal behaviour are also included, then all our patients had some clear neurological abnormality on admission. Indications of a more terminal illness, such as coma and cerebral herniation, were not seen in any of our children, although three had a hemiparesis, which Wald *et al* describe as a late sign.[5]

Diagnosis took between one and three weeks from the onset of symptoms in all children, due to a combination of a delay in presentation to hospital, and delay in recognition at this hospital or the referring one. Sinusitis was evident on initial scan or radiograph in all cases, but in five cases the initial computed tomogram did not show empyema. A collection took one to two weeks to show with repeated scanning. It is uncertain whether the empyema developed later or whether a small early collection was missed on the initial scan. Early or small collections may be missed for a variety of reasons. In previous years early abscesses were less often established with the poor scanning quality and slow scan times of the first computed tomography machines, without high quality resolution capabilities. Interpreter errors of more subtle findings may occur. Early suppuration is isodense, but other changes may help such as 'mass effect' from associated cerebral oedema.[5] Finer 3–5 mm slices may be necessary rather than the more routine 10 mm ones. It is, however, still well recognised that abnormal findings on computed tomography may develop within one to seven days of a normal scan, and repeated scans are necessary if the diagnosis is still suspected.[2] Luken and Whelan describe four cases who had a subdural empyema demonstrated by angiography or operatively, within 24 hours of a normal computed tomogram.[6] It is not known whether magnetic resonance imaging would be more sensitive than computed tomography in diagnosing subdural empyema in these cases. Resolution has been reported to follow medical treatment alone,[2] but this is rare and has also been linked to increased mortality.[7] Some form of surgical drainage is usually required. Burr holes and irrigation may be sufficient in some cases, but craniotomy will frequently be required to give the best chance of resolution with least chance of further intervention being necessary. For example, Johnson *et al* reported 13 children with sinusitis induced subdural empyema.[8] All of the 10 who were initially medically treated developed radiological evidence of disease progression and seven had persisting signs. All improved after surgical drainage. Our series supports these observations.

The outlook in our small series was good. There were no deaths compared with a reported mortality of 18–40%.[1 3 8] Residual neurological sequelae were uncommon, occurring in only three of our children, and resolving with time in two.

Subdural empyemas will usually present to general paediatricians. Because the initial symptoms can be non-specific, the diagnosis can easily be overlooked and correct treatment delayed. Clinical suspicion of subdural empyemas should be highest in young adolescent children with a pyrexia of unknown origin that is associated with any neurological abnormality and symptoms or signs suggestive of sinusitis. Evidence from radiography or computed tomography of sinusitis should prompt repeated scanning of the head over the next few weeks until symptoms resolve or a diagnosis is made. Early diagnosis, treatment, and awareness of this rare but important condition are the mainstay of successful outcome.

We thank Drs Besser and Johnston for allowing us to report their patients.

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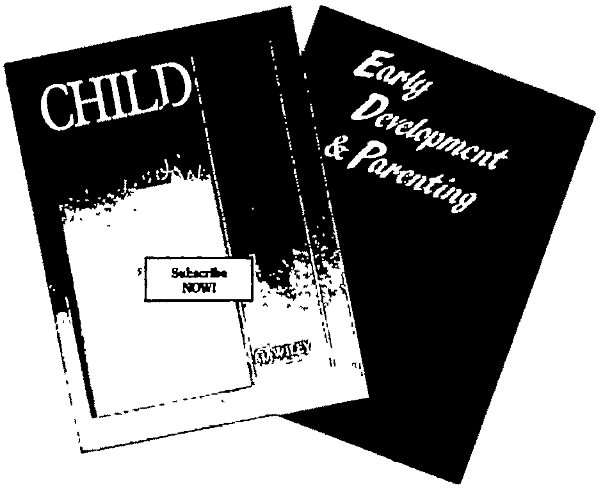

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G Owen, P W Buss, H R Jenkins, A H Goodwin, M C Goodchild

Abstract

A father and son with profound reduction of exocrine pancreatic activity and little visible pancreatic tissue on ultrasound or computed tomography are described. Both have some degree of liver disease, which is more marked in the son. The disorder, apparently familial, does not correspond to any reported previously.

(*Arch Dis Child* 1992;67:1481–2)

Although there are numerous causes of pancreatic exocrine insufficiency in childhood, cystic fibrosis is responsible for the vast majority, followed by Shwachman's syndrome.[1 2] Other causes, including those with a familial incidence, are rare. We describe a father and son who have pancreatic enzyme insufficiency and abnormal liver function. We believe this may represent a new disorder.

Case reports

CASE 1

A 3 year old boy presented with a history of steatorrhoea since birth, frequent episodes of rectal prolapse, and generalised pruritis. There were no dysmorphic features. Height and weight were just below the 97th and on the 75th centile respectively. Positive findings were excoriation marks, slight abdominal distension, and a reducible rectal prolapse. Stools were cream coloured and loose. Faecal fat was raised at 12·3 g/day. Sweat electrolytes were normal, as were repeated full blood counts, including differential white cells counts. Neurophil function tests and a comprehensive immunological screen were normal. Serum amylase and immunoreactive trypsin were low. The tocopherol:cholesterol ratio was low, while fasting liver enzymes and total serum bile acid concentrations (TSBA) were high (table 1). The bilirubin concentration was normal. Pancreatic function testing revealed very low or absent values for lipase, trypsin, and amylase, both fasting and after intravenous pancreozymin and secretin (2U/kg each).

A jejunal biopsy specimen and skeletal survey were normal. Ultrasound scan and computed tomography of the pancreas revealed only a small amount of normal tissue located in the head and tail.

He was given daily vitamin supplements and pancreatic replacement treatment that produced a decrease in faecal fat excretion to 5·7 g/day and gradual disappearance of the rectal prolapse. However results of liver function tests remained abnormal (table 1). Further investigations for possible causes of liver disease, both infective and metabolic, including a liver biopsy with examination by light and electron microscopy, were all normal. An endoscopic retrograde cholecystopancreatogram (ERCP) showed normal pancreatic and common bile ducts but little contrast medium passed into the common hepatic and intrahepatic ducts—possibly due to a stricture of the common hepatic duct, but it was impossible to exclude compression by the endoscope. The small amount of contrast within the intrahepatic ducts showed normal ducts.

The boy has been followed up to age 8 and has remained clinically well and the pruritis and scratching have ceased. Results of liver function tests continue to show an improvement but remain abnormal (table 1).

CASE 2

The father of case 1, born in 1955, also gave a lifelong history of loose fatty stools and pruritis. He had been investigated at ages 5 and 18 years and found to have a raised faecal fat excretion, a low serum calcium and normal full blood count, sweat electrolytes and liver function tests, though γ-glutamyltransferase was not measured. A Lundh test meal had shown a marked

Table 1 Results of blood tests in case 1. Normal values are given in square brackets

Date	Aspartate transaminase [5–45] (IU/l)	γ-Glutamyl-transferase [0–45] (IU/l)	Alkaline phosphatase [30–350] (IU/l)	Calcium [2·26–2·6] (mmol/l)	Vitamin A [0·7–1·5] (μmol/l)	α-Tocopherol cholesterol ratio [>2·2] (μmol/mmol)	TSBA [<15] (μmol/l)
4/8/87	225		656	2·1	0·94	1	
Started pancreatin*							
28/9/87	406	302	787	2·38	1·8	2·4	34
Started vitamins A, B, C, and E†							
9/12/87	374	260	774	2·23			129
23/6/89	140	153	534	2·08	1·06	4	
Started alfacalcidol							
12/6/90	145	137	445	2·25	0·94	2·2	
12/5/92	109	89	354	2·25	1·02	3·8	55

*Creon (Duphar); †vitamins A, B, and C given as Abidec (W-L)

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Table 2 Results of blood tests in case 2 Normal values are given in square brackets

Date	*Aspartate transaminase [5–45] (IU/l)*	*γ-Glutamyl-transferase [0–45] (IU/l)*	*Alkaline phosphatase [30–110] (IU/l)*	*Calcium [2·26–2·6] (mmol/l)*	*Vitamin A [0·9–2·5] (μmol/l)*	*α-Tocopherol: cholesterol ratio [>2·2] (μmol/mmol)*	*TSBA [<15] (μmol/l)*
28/9/87	40	90	125	2·5	2·7	1·3	13
Changed to pancreatin as Creon							
22/11/88	40	109	103		2	0·7	
Started vitamin E							
16/5/89	42	62	137	2·15	2·08	4·0	21
7/5/91	81	119	97		2·0	5·2	40
12/5/92	36	60	75	2·08	1·63	4·3	16

reduction of all three major pancreatic enzymes; pancreatic scan revealed no normal pancreatic tissue and the diagnosis was exocrine pancreatic insufficiency. He was treated with pancreatin as Nutrizym (Merck) tablets, vitamins A and D, and calcium supplements; alfacalcidol had been added later. He improved and at the time of his son's presentation he had no specific complaints. Bowel actions were 1–2 times daily, usually formed but somewhat bulky and pale in colour. General examination was normal with height and weight on the 75th centile. There was no visible pancreatic tissue on ultrasound or computed tomography. Repeated full blood counts and tests of neutrophil function were normal. A glucose tolerance test showed normal insulin concentrations, but the two hour blood glucose concentration was raised at 7·6 mmol/l. Values for serum amylase and immunoreactive trypsin were low. Serial tests of liver function (abstaining from alcohol) with measurements of fasting TSBA and vitamin concentrations are shown in table 2. Detailed investigations for possible causes of liver disease were normal, though an ERCP and liver biopsy were not performed. Pancreatic enzyme replacement treatment was changed to Creon (Duphar) with further improvement in stool character, and vitamin E supplementation was given.

A paternal uncle of case 2, who had died at the age of 62 had been underweight, suffered diarrhoea all his life, and scratched excessively. No hospital tests or biochemical measurements had been performed.

Discussion

Investigations of this father and son with exocrine pancreatic insufficiency and abnormal liver function tests have excluded cystic fibrosis, Shwachman's syndrome, isolated pancreatic enzyme deficiencies, malnutrition, and congenital pancreatic hypoplasia.[1–3] Partial exocrine pancreatic insufficiency has been described in association with paucity of interlobular bile ducts,[4] but severe failure to thrive is an important feature of children with this disorder; in addition, there are characteristic changes on a liver biopsy specimen that were not seen in case 1.

There may be an association between sclerosing cholangitis and chronic pancreatitis in adults[5] and between sclerosing cholangitis and inflammatory bowel disease in childhood.[6] Neither of our patients has evidence of inflammatory bowel disease and sclerosing cholangitis with chronic pancreatitis has not been reported in childhood. An attempt to confirm or refute such an association by performing an ERCP in case 1 was only partially successful due to technical problems and it was felt unethical to repeat this.

Both patients have raised TSBA in the fasting state, a finding more marked in the son. The meaning of this is unclear, but it may be a reflection of the underlying liver disease.

Follow up over five years has shown a considerable improvement in liver function test status, especially in the son, since the introduction of pancreatic enzyme and vitamin supplements; which suggests that this may be associated with correction of malabsorption. The son's present results are not dissimilar from those of his father, allowing for normal age related variation, and we conclude that both patients have the same disorder.

We thank Professor J Rhodes and Dr R Lewis for permission to report the findings of case 2 and Mr Y Qureshi for measurement of total serum bile acid concentrations.

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Thrombolysis with low dose tissue plasminogen activator

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Abstract

Two cases of vena caval thrombosis in infants were successfully treated with low dose (0·01–0·05 mg/kg/hour) local infusions of tissue plasminogen activator after conventional anticoagulant treatment had been unsuccessful. This approach is useful for clots associated with indwelling intravascular catheters, and a low dose infusion of tissue plasminogen activator as a regional application is recommended to achieve clot lysis with minimal systemic effects.

(*Arch Dis Child* 1992;67:1483–4)

Recombinant tissue plasminogen activator has been used in adults for thrombolysis after myocardial infarction.[1] There is little experience of its use in children and there are no dose recommendations. Two cases of vena caval thrombosis in infants are reported here in which conventional anticoagulant treatment was unsuccessful but which were successfully treated with low dose (0·01–0·05 mg/kg/hour) local infusions of tissue plasminogen activator.

Case reports

CASE 1

A neuroblastoma was removed from a 13 month old boy. A Hickman line was sited in the left internal jugular vein to administer chemotherapy. Two weeks later he develoepd oedema and venous congestion of the face, neck, and arms. An ultrasound examination showed obstruction of the superior vena cava and a diagnosis of superior vena caval thrombosis was made.

Treatment was started with an infusion of heparin at 25 IU/kg/hour following a bolus of 100 IU/kg. There was no clinical improvement after 24 hours. A venogram showed an extensive thrombus filling the left subclavian and innominate veins extending into the superior vena cava.

An infusion of recombinant tissue plasminogen activator was started through the Hickman line at a dose of 0·01 mg/kg/hour. This was increased to 0·05 mg/kg/hour after four hours, and after 24 hours of treatment improvement in the swelling and oedema was noted. An ultrasound examination showed blood flow through the innominate veins and superior vena cava.

After 48 hours of treatment there was some bleeding from the Hickman line insertion site. The infusion of tissue plasminogen activator was stopped for three hours and restarted at 0·03 mg/kg/hour. No further bleeding was seen. After three days of treatment the tissue plasminogen activator infusion was stopped, the Hickman line removed, and a heparin infusion started. During treatment fibrinogen was measured daily and was always greater than 3·5 g/l. The concentration of the D-dimer during treatment was between 0·2 and 4 mg/l.

CASE 2

A male infant was born with transposition of the great arteries and had an atrial septostomy on the first day of life. This was followed one week later by a switch operation with reimplantation of the coronary arteries. His clinical course after the operation was complicated by persistent bilateral chylothoraces and he needed albumin and total parenteral nutrition via the central venous cannulae. Four weeks after the operation a clinical diagnosis of superior vena caval thrombosis was made and confirmed by venography. During this period there had been continuous cannulation of the superior vena cava by several different catheters inserted by different routes. The child was treated with an intravenous infusion of heparin and then warfarin by mouth to achieve an internationalised normal ratio of 2·0–2·5.

Six weeks after the operation an ultrasound examination of the inferior vena cava showed a large thrombus extending from the tip of a right femoral vein catheter and occupying most of the inferior vena cava. Warfarin was discontinued and recombinant tissue plasminogen activator given through the femoral vein catheter at an initial dose of 0·01 mg/kg/hour. This was increased to 0·02 mg/kg/hour after six hours and was continued for six days. Serial ultrasound examinations showed complete lysis of the clot over this period. The infant was then treated with an intravenous infusion of heparin followed by warfarin by mouth.

There was no bleeding during the infusion of tissue plasminogen activator. The fibrinogen concentration was always greater than 1·5 g/l and the D-dimer concentration between 0·2 and 4 mg/l.

Discussion

Tissue plasminogen activator is a naturally occurring protein which plays a part in the fibrinolytic cascade. It catalyses the conversion of the inactive proenzyme plasminogen into the active serine protease plasmin. Tissue plasminogen activator has a high affinity for fibrin and the tissue plasminogen activator-fibrin complex enhances the binding of plasminogen to fibrin. This fibrin bound plasminogen is broken down to produce plasmin locally at the site of the clot. This clot selective mechanism, together with the low affinity of tissue plasminogen activator for circulating plasminogen, is thought to minimise the systemic thrombolytic effects of tissue plasminogen activator.

Bleeding may be reduced by the regional application of tissue plasminogen activator directly onto the clot with the assumption that the thrombolytic effect will be entirely local. This is attractive for clots associated with indwelling intravascular catheters which may be used as the treatment route.

Our two patients received a low dose infusion of tissue plasminogen activator as a regional application to try to achieve clot lysis with minimal systemic effects.

A similar low dose (0·05 mg/kg/hour) regional infusion of tissue plasminogen activator has been used in four neonates with caval thrombosis secondary to indwelling intravascular catheters.[2] There was successful lysis of the clot in three of the patients. In one patient the infusion caused a decrease in fibrinogen concentrations and an increase in fibrin degradation products and this infant had an intraventricular haemorrhage.

When higher doses of tissue plasminogen activator (0·1–0·5 mg/kg/hour) were given to 12 children,[3] six had bleeding complications. In these six patients bleeding was associated with a tissue plasminogen activator dose of 0·46–0·50 mg/kg/hour).

The age of the clot to be lysed has an important effect on its susceptibility to thrombolysis. Most in vivo studies suggest that clots become more resistant to lysis as they age.[4] Early initiation of treatment is important and this may have been a factor in the success of the low doses of tissue plasminogen activator reported here.

Although pharmacologically effective doses of tissue plasminogen activator appear to cause less of a systemic lytic effect than streptokinase,[5] there is a poor correlation between markers of systemic thrombolysis and bleeding complications.[6]

In view of the limited experience with the use of tissue plasminogen activator in children and the fact that these patients are likely to have a relatively high incidence of catheter associated thrombosis, our patients indicate that local application of low dose (0·01–0·05 mg/kg/hour) infusions may be a useful approach.

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Fatal encephalitis/encephalopathy in primary human herpesvirus-6 infection

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Abstract

An encephalitic illness with a fatal outcome occurred in a 9 month old girl with virologically confirmed exanthem subitum. Human herpesvirus-6 (HHV-6) DNA was found in the cerebrospinal fluid at the acute stage of the disease by the polymerase chain reaction, but the virus antigen was not detected in her brain tissue. This suggests that HHV-6-induced encephalitis/encephalopathy may be due to a non-infectious process.

(*Arch Dis Child* 1992;67:1484–5)

Central nervous system complications are well known during the course of exanthem subitum, which is caused by primary infection with human herpesvirus-6 (HHV-6). It has been strongly suggested that the virus invades the central nervous system and causes encephalitis or encephalopathy.[1 2] There is, however, little information on whether the virus invades the brain tissue. We report a fatal case of exanthem subitum with encepalitic illness that occurred in the pre-eruptive stage of the disease. The virological and histopathological findings of the case are also presented.

Case report

A 9 month old girl was admitted to the Kariya Sogo Hospital because of high fever and generalised clonic convulsions. She had been apparently well until the afternoon of the previous day (day 0) when her temperature had suddenly risen to 39·2°C. In the early hours of the next morning she had a generalised clonic convulsion that persisted for one minute; this occurred approximately 10 times during the next four hours. She vomited several times and became drowsy and was admitted to our hospital suffering from stupor that morning (day 1). On admission, physical examination revealed a well nourished, well developed infant with a normal anterior fontanelle. She had been born at full term after an uncomplicated pregnancy. Her temperature was 38·6°C. A computed tomogram and electroencephalogram showed normal results. Her cerebrospinal fluid was examined; the concentrations of protein and glucose were normal and there was no pleocytosis. White cell count was $2{\cdot}5\times10^9$/l with 19% lymphocytes. Other haematological and blood chemical analyses showed normal values except for a mild increase in her liver enzymes. She was treated conventionally for encephalitis and with acyclovir (30 mg/kg/day) because herpes simplex virus encephalitis was clinically suspected on her admission. Despite the treatment, her consciousness level worsened and she was assisted by mechanical ventilation. On day 3 of the illness her temperature returned to normal and a rubella-like skin rash appeared on her face and trunk. On the same day her brain function could not be detected by electroencephalography. Cranial computed tomography performed on day 8 of the illness demonstrated subarachnoidal bleeding, appreciable brain oedema, and diffuse hypodensities. On day 21 of the illness she did not respond to the usual cardiopulmonary resuscitative efforts. After parental permission was obtained, a piece of brain tissue was taken by needle biopsy.

Methods

HHV-6 was isolated by cocultivation of peripheral blood mononuclear cells (MNCs) from the patient with MNCs from cord blood, and antibody titres to HHV-6 were tested by the neutralisation test, as described previously.[3] Antibody titres to HSV types 1 and 2 were measured by the standard 50% plaque reduction neutralisation tests using the vero cell culture system.

HHV-6 and herpes simplex virus DNA were extracted from the cerebrospinal fluid and amplified by the nested polymerase chain reaction (PCR) using procedures reported elsewhere.[4]

HHV-6 antigen in the brain tissue was examined by enzyme immunoassay using monoclonal antibodies to HHV-6 as described elsewhere.[5]

Results

HHV-6 was isolated from blood obtained on day 1 of the illness, but not from blood on days 5 and 18. HHV-6 DNA sequences were detected in the cerebrospinal fluid obtained on day 1 of the illness by the PCR. There was a significant rise in the antibody titres to HHV-6 from day 1 (<4) to day 5 (128) and day 18 (>512) of the illness. On the other hand, there was no evidence of primary herpes simplex virus infection in blood and cerebrospinal fluid samples.

In the brain tissue obtained just after her death there was no infiltration of inflammatory cells nor HHV-6 antigens.

Discussion

Several cases have been reported showing central nervous system complications in association with primary infection with HHV-6 in which it has been suggested that the central nervous system has been invaded by the virus.[1 2] Yamanishi *et al*, however, have reported that the virus DNA could have been amplified in seven (70%) of 10 samples of cerebrospinal fluid from patients with exanthem subitum who had convulsions or a bulging fontanelle, or both.[6]

It is important to note that in the present study the brain tissue obtained just after death did not have any inflammatory cells and there was no HHV-6 antigen despite the fact that HHV-6 DNA was clearly detected in her cerebrospinal fluid sample. Oedematous changes and the hypodense areas of the brain observed by computed tomography in our case and in other reported cases suggest encephalitic changes of the brain. However, the findings in the brain tissue of our case do not support this speculation. If enough (or the entire) brain sample had been available in our case we might have been able to ascertain the relationship between the histological findings and the distribution of HHV-6 antigen more precisely. Moreover, in order to confirm the encephalitogenic nature of the virus, localisation of HHV-6 antigen or the virus gene sequence in brain tissue would need to be shown by using sensitive and specific techniques.

It is generally believed that exanthem subitum is a common benign infectious disease and the prognosis is uniformly excellent even for cases complicated by convulsive seizures. However, although the case reported here is a rare complication of exanthem subitum, it is important for physicians who care for patients with exanthem subitum to be aware of the potential hazard of unexpected death.

Recombinant human interleukin-2 was kindly supplied by Takeda Chemical Industries Ltd, Osaka, Japan

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Recovery of protein from urine specimens collected in cotton wool

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Abstract

Cotton wool balls have been used to aid the collection of urine from infants. Concentrations of two urinary proteins, albumin and retinol binding protein, decreased by 40 and 80% respectively within 15 minutes of contact with the cotton wool. Cotton wool balls should not be used when investigating proteinuria.

(*Arch Dis Child* 1992;67:1486–7)

Examination and analysis of urine is an important part of the management of a wide variety of medical disorders. Although obtaining urine specimens from older children is a relatively simple procedure, collecting specimens from infants is often less satisfactory. A urine bag may be required and this can be difficult to apply, particularly in girls, with repeated applications liable to cause discomfort. In an attempt to overcome this problem, it has been suggested that urine can be successfully collected in this age group by cotton wool balls held in suitable disposable nappies.[1, 2] This method of collection has been shown not to interfere with the measurement of a number of urinary constituents (sodium, potassium, nitrogen, creatinine, urea, amino acids), though calcium and phosphorus concentrations are increased.[1] The validity of this method of collection has not been established for proteins, however, which are commonly investigated in the assessment of renal disease. We therefore looked at the effect of cotton wool on the concentrations of two commonly measured urinary proteins, retinol binding protein and albumin.

Method

Urine specimens were obtained from normal children and those with glomerular or tubular dysfunction to obtain urine samples with a wide range of retinol binding protein and albumin concentrations. A 20 ml specimen of urine was mixed and then divided into five equal aliquots, four of which were placed on standard cotton wool balls. The urine was then extracted from the cotton wool after 15, 30, 60, and 120 minutes of incubation at room temperature, by compressing the cotton wool ball in a 20 ml syringe. Fourteen specimens were examined with respect to retinol binding protein (concentration range 43–24 000 µg/l) and albumin (concentration range 3·8–72 400 mg/l). The specimens were then stored at −20°C for up to four weeks before assay. Retinol binding protein was determined using an enzyme linked immunosorbent assay (ELISA)[3], albumin by a radioimmunoassay, and creatinine by a modified Jaffé reaction.

The results were analysed using a two tailed *t* test.

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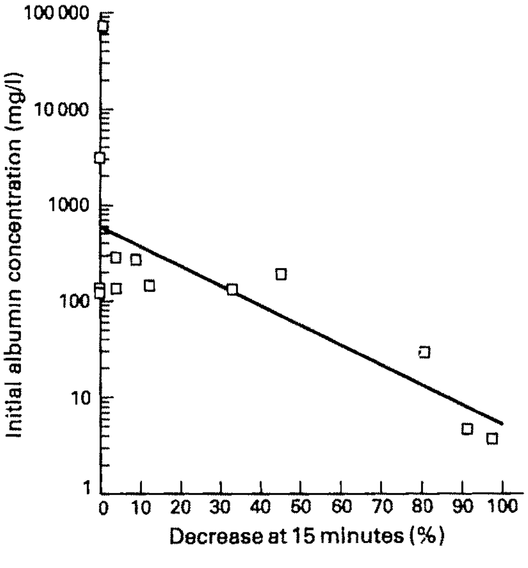
Results

As with previous studies, there was no effect on the determination of creatinine concentration in the urine specimens after contact with cotton wool. The precision of the assays are shown in the table.

There was a significant decrease of 35–40% ($p<0{\cdot}05$) in the albumin concentration, though this was not consistent and a number of specimens showed only a slight loss of albumin. The greatest percentage decreases were seen in urine specimens of lower albumin concentrations

Precision of ELISA for determination of urinary retinol binding protein and of radioimmunoassay for urinary albumin concentrations

Measurements	*Mean (SD)*	*Coefficient of variation (%)*
Retinol binding protein.		
Within run (n=10)	78 6 (3·8)	4·9
Between run (n=14)		
(i)	46·2 (7·2)	15 5
(ii)	133 0 (12·2)	9·2
Albumin:		
Within run (n=10)		
(i)	4 9 (0·5)	9·9
(ii)	162·0 (9·4)	5·8
Between run (n=13)		
(i)	4·7 (0·4)	9·0
(ii)	153·6 (8·6)	5·6



Relationship between decrease in albumin concentration measured and initial concentration of albumin. Pearson's $\rho_r=-0{\cdot}7099$, $p=0{\cdot}004$.

with an inverse relationship between the percentage decrease at 15 minutes and the initial albumin concentration (figure).

The decrease in retinol binding protein concentration was greater and consistent, amounting to a loss of 80% of the measurable retinol binding protein ($p<0\cdot001$). The loss occurred within the first 15 minutes of contact with the cotton wool, was less dependent on the initial retinol binding protein concentration, and did not significantly change over the next 105 minutes.

Discussion

The difficulties of obtaining urine specimens from infants is well known and attempts to make collection easier are welcomed. The use of cotton wool balls to ease collection of urine for the determination of low molecular mass urinary constituents has been shown to be reliable. We feel, however, that it would be unwise to extend this practice to the collection of urine specimens for the measurement of proteinuria. The fibres used in the manufacture of cotton wool balls appear to absorb at least part of the protein content of the urine and make meaningful measurements impossible.

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TYPES OF PSYCHIATRIC TREATMENT

Drug treatment

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There is general agreement that psychoactive drugs should only be given as part of an overall treatment plan. It might be thought there would also be general agreement that the use of psychoactive drugs should be informed by the literature but there are such large differences in prescribing practice between clinicians and between countries that other factors must be relevant. Stimulant drugs are probably the best investigated and best understood psychoactive drugs in use in childhood and yet they are seldom prescribed in Britain, where drugs are frequently used to treat sleep problems and nocturnal enuresis.[1 2] Both of these conditions are more appropriately managed with behavioural methods. On the other hand, some severe psychiatric problems are unusual and little researched in childhood or adolescence. One can appeal to the adult literature but it may not be relevant. There are a number of recent reviews of pharmacotherapy which differ in emphasis and which are helpful in whole or in part.[3–7]

There is still quite a gap between our knowledge of what drugs can do biochemically and why they make some problems better. Most psychoactive drugs affect more than one neurotransmitter system,[8] so this account leaves neurotransmitters aside and matches operationally defined syndromes with drugs believed to alter target symptoms within these syndromes.

Sleep problems

Difficulty in settling, 'midnight intruder', and dawn rising are common sleep problems in the toddler years and respond well to behavioural methods, which are the treatment of choice.[9] Prescription of hypnotics to children is contraindicated by the *British National Formulary*[10]; despite this, their use is widespread.[1] Trimeprazine (Vallergan, Rhône-Poulenc Rorer) works well in the short term[11] and may be used in a crisis, for example, when parents are severely sleep deprived themselves. Tolerance develops rapidly and if the response is to increase the dose the child may become zombie-like and drool throughout the day. Data sheets for Vallergan now contain an expanded section on the risk of tardive dyskinesia, which is another reason for caution. Chloral is an alternative for short term use. Benzodiazepines are best avoided in childhood because of their behavioural toxicity.

Occasional nightmares are common and can usually be related to a frightening experience. If frequent they should be inquired into. Night terrors, sleep walking, and sleep talking are parasomnias and often respond to explanation and reassurance.[12] When they are frequent and occur at a predictable time of the night, they can sometimes be controlled by pre-emptive waking.[13] Drug treatment is rarely necessary. Low dose benzodiazepines have been used and there are reports of successful use of both imipramine[14] and carbamazepine[15] which may be preferred.

Narcolepsy and other hypersomnias are seldom diagnosed in childhood. Psychostimulants, for example, methylphenidate or dexamphetamine, and more recently mazindol,[16] are favoured in the adult literature. Clomipramine may reduce the frequency of narcoleptic attacks and of cataplexy which is loss of tone without loss of consciousness.[12] Dietary tyrosine supplements have been found helpful in reducing hypersomnia in adults in some hands[17] but not in others.[18] Quantitative serum tyrosine monitoring is prudent in childhood.

Confusion and delirium

Confusion and delirium are medical emergencies and this is the first line of management. Fever or other signs may point to a medical cause and non-convulsive status epilepticus is one of many conditions that must be considered. Drugs may be responsible, whether medically prescribed or illicitly obtained, through idiosyncratic reaction or overdose.

When a drug is responsible for the reaction, it should be stopped where possible. Disorientation and behaviour disturbance are often more prominent at night and chloral is effective if only night sedation is required.

Where behaviour disturbance is jeopardising treatment, the short term use of chlorpromazine is recommended, in doses sufficient to confine the child to bed, combined with adequate illumination and sensitive nursing care. Such reactions are usually shortlived.

Children with dementing illnesses associated with behavioural problems may rarely require chronic sedation, for example, chlorpromazine or thioridazine which should be prescribed in the lowest dose effective and in higher dose at night if night time sedation is also required. The oral route is preferred as intramuscular injections may be interpreted as attacks. Where tablets are not tolerated and when thiordazine is chosen, the suspension should be used as the liquid is extremely unpalatable.

Schizophrenia, hallucinations, and neuroleptic drugs

Schizophrenia of adult type is rare in prepubertal children, although it becomes more common in adolescence. Its management is a specialist matter and will often involve inpatient treatment in a dedicated unit. An underlying physical disorder should always be sought. Treatment is symptomatic and based upon the symptoms present at the time.

As drug treatment hinges upon neuroleptics with their attendant long term risk of tardive dyskinesia, non-drug alternatives can and perhaps should be tried where appropriate, although it is recognised that most units do not do this.

Auditory hallucinations may respond to an ear plug.[19] It should be placed in the more impaired ear where there is a difference, and when the patient will tolerate it. Visual hallucinations are usually paroxysmal and distorting spectacles interfere with them if the patient can be persuaded to sit down and use them. Both these types of hallucinations can occur in plain consciousness in the absence of psychosis.[20 21] In these circumstances, compliance with the treatments suggested above may be easier to obtain.

The drug treatment of children and adolescents with schizophrenia is little researched and practice is based upon analogy with the adult literature.

It is important to appreciate the huge differences in potency between neuroleptics. A dose of 100 mg of chlorpromazine is equivalent to 100 mg of thioridazine, but 5 mg of trifluoperazine and only 2 mg of haloperidol and only 2 mg of pimozide, but 200 mg of sulpiride and 40 mg of clozapine. In general, the more potent neuroleptics carry a greater risk of extrapyramidal side effects and the less potent neuroleptics are more sedative, but still have extrapyramidal side effects. Dependent upon the degree of disturbance at presentation, sedation may be the first priority. Otherwise, a period of drug free inpatient observation by experienced staff is preferable and may be all that is required in some brief psychotic episodes.

Subsequent management in those requiring medication will comprise a systematic trial of several weeks of a drug from each of the various groups given individually according to tolerance. Typical representatives would be chlorpromazine, thioridazine, sulpiride, and haloperidol. Depot neuroleptics are usually avoided until a stable response has been obtained, if they are to be used at all.

Unfortunately, a therapeutic margin between symptom relief and side effects can be hard to find in the prepubertal patient.[22] Clozapine offers hope for treatment resistant patients but it is only licensed for use in children older than 12 years subject to compliance with an expensive monitoring procedure to guard against agranulocytosis.[23]

Drug treatment mainly affects the positive symptoms of hallucinations and delusions. It has very little effect on the negative motivationless state that some patients are left with. Ciompi has drawn attention to the various patterns of schizophrenic illness.[24] Only some forms imply 'medication of life'. Once control is achieved, a decision must be made whether to try the patient on a diminished drug dosage while still in hospital, or after safe return home. The issue of continued treatment should be kept under continual review. Antiparkinsonian agents are not prescribed routinely but are only given if the relevant side effects occur.

Patient and parents must be warned of the possibility of writhing, dystonic movements of the face and body, and oculogyric crisis in the first few days of treatment with neuroleptics and of parkinsonian symptoms of tremor, rigidity, akinesia, and salivation in the succeeding weeks. All of these symptoms respond to antiparkinsonian agents or medication reduction. Acute dystonic reactions are distressing and they are medical emergencies. Parents of children who are managed as outpatients may be given a few procyclidine tablets or equivalent to use, if required, pending attendance at a casualty department. Intramuscular injection of an antiparkinsonian drug will bring more immediate relief.

Some patients experience akathisia, an unpleasant restless agitation, usually within the first two months of starting a neuroleptic. It can be difficult to treat without drug reduction. Adult work indicates akathisia is relatively resistant to antiparkinsonian drugs but propranolol may be helpful. Clonazepam has been shown to be effective in some adolescent cases.[25]

More seriously, neuroleptic malignant syndrome may present at any time.[26] In its florid state it is characterised by fever, fluctuating consciousness, autonomic instability, increased tone, and raised serum creatinine kinase. Formes frustes occur and fever or raised enzymes may be lacking. It is a potentially lethal condition. Neuroleptics must be stopped at once. Symptoms may take a week or more to respond but longer if the patient has taken a depot neuroleptic.

Dantrolene and bromocriptine have been used but the essence of treatment is attention to fluid balance and cardiorespiratory support in a medical setting.

Tardive dyskinesia is an important long term risk of neuroleptic treatment. It may be transient and appear as a withdrawal dyskinesia lasting from days to several months, or it may be persistent. In tardive dyskinesia irregular choreoathetoid movements occur predominantly in the buccal-lingual musculature and at the distal extremities. It is not uncommon in children exposed to neuroleptic, 25% in one series.[27] Mentally retarded patients are at greater risk and also at greater risk of neuroleptic treatment. Tardive dystonia is a more malignant variant characterised by sustained contraction of skeletal musculature, manifest as, for example, sustained tongue protrusion, disabling posturing, stridor from laryngospasm, and dysarthria.[7 28] In addition, Gualtieri has described a late onset behavioural equivalent of tardive dyskinesia that he terms tardive akathisia with dysphoria and motor restlessness.[7]

All these conditions are difficult to treat beyond withdrawal of neuroleptics and waiting. They may be irreversible but remission rates in children are fortunately higher than in adults.

Non-extrapyramidal side effects of neuroleptics include gynaecomastia, galactorrhoea, amenorrhoea, weight gain, and jaundice. Chlorpromazine is particularly associated with photosensitive reactions and thioridazine with a pigmentary retinopathy in high dose.

Hypomania and bipolar illness

Hypomania is characterised by elevated mood, excitement and irritability, pressure of talk and flight of ideas, which are often grandiose. Teenagers are disinhibited and sleep little. Mania is a more florid version of the same. It is rare, even reportable before the teenage years.[29] In the acute phase, sedation with a major tranquilliser and hospital admission may be required. Hypomanic episodes may be recurrent, or more usually part of a bipolar illness. Children and teenagers with bipolar disorders have recurrent episodes of severe depression and hypomania. Lithium carbonate is the treatment of choice.[6 30] Because of differences in bioavailability, it is important to choose a preparation and stay with it.

Sustained release lithium carbonate can be given twice daily and blood concentrations are monitored in the steady state, 12 hours after the previous dose. In practice this means about five days after the last dose increase. Target serum concentrations are usually within the range of 0·6–1·0 mmol/l. When control is obtained, measurements are repeated every six weeks or so and also thyroid function tests and tests of renal function are performed—less frequently but more often if there is cause for concern. Fluid loss through vomiting, diarrhoea, and sweating in hot weather can all cause toxicity that is characterised by diarrhoea, vomiting, tremor, ataxia, dysarthria, and muscular weakness progressing to cardiac arrhythmia, stupor, and death if lithium is continued. Less severe side effects include polydipsia, polyuria, weight gain, and thyroid dysfunction. Previous worries about nephrotoxicity seem to have been exaggerated.[31]

In rapid cycling bipolar illnesses there are three or more occurrences within a year. Sometimes there may be several mood swings within a week. Carbamazepine can be used as an alternative to lithium carbonate in unresponsive patients and as a treatment of choice in rapid cycling patients.[32] Dosages are the same as in the treatment of epilepsy and the sustained release preparation is preferred.

Depression

Depression of adult type is increasingly recognised in childhood. In the past it was probably included in the category of emotional disorders without further inquiry.

When suspected, the child must be interviewed alone and suicidal ideas inquired after. A decision should be made whether referral for inpatient treatment is required. Although child psychiatrists use antidepressants to treat more serious depressions[2] evidence to support this practice is so far lacking from double blind trials and the issue is unresolved. There is little experience with the new antidepressants.

Typically, amitriptyline is used for its sedative effect in the agitated patient and imipramine is used for its more stimulant effect in the patient who has slowed up. Patients and parents should be warned about the early appearance and resolution of the anticholinergic effects of dry mouth, constipation, and blurred vision. These are not usually problematic if the drug is introduced slowly. Children seem to require 75–100 mg daily on average and starting at 25 mg at night, the dose can be increased by a similar increment every three days or so.

The antidepressant effect is not usually obtained before about 10 days of treatment at the appropriate dose. In treatment responders antidepressants are usually continued for about three months after response is obtained. I do not usually begin withdrawal of drugs at critical times, for example, at the start of the new school year. Intersubject absorption of imipramine varies considerably and monitoring of blood concentrations is recommended when this tricyclic is used. Puig-Antich *et al* have suggested that a total plasma concentration of 150 μg/l (imipramine and desipramine) is necessary for therapeutic effect.[33] Serial electrocardiographic (ECG) records are recommended if high doses of imipramine are needed to achieve this.[6] Clearly, parents must understand the need to supervise the taking of tablets and to keep them away from the patient and younger siblings. Childproof containers are essential.[34]

Sleep deprivation or deprivation of rapid eye movement sleep as treatments for depression have yielded inconsistent results but may offer a treatment alternative for antidepressant resistant patients.[35 36]

Very severe depressive illness unresponsive to antidepressants, depressive stupor, and catatonic stupor are rare indications for electroconvulsive treatment. It should not be undertaken without further supportive consultant opinions, perhaps from colleagues in adolescent psychiatry and adult psychiatry, in addition to the usual thorough discussion with patient and parents. The great advantage of electroconvulsive treatment is rapid relief when it is successful.[37]

Obsessive compulsive disorders and trichotillomania

The manifestations of obsessive compulsive disorder include repetitious checking and other rituals and compulsions which often involve the whole family. Children who are severely handicapped by these symptoms may require inpatient treatment.

Behavioural management has a role but it is less powerful in this condition than was originally thought. Clomipramine is effective, even in the absence of coexisting depressive symptomatology.[38 39] Trichotillomania responds to the same drug,[40] but this should not be taken as evidence that the nature of these two conditions is similar.

Tics and Tourette's syndrome

Simple motor tics are widespread, transient, and can usually be managed with explanation and reassurance. The syndrome of Gilles de la Tourette comprises multiple motor tics and phonic tics. Medication is only indicated when the tics are intrusive and handicapping. There is no evidence that early treatment modifies the course of the disease.

Haloperidol is best researched and often cited as the treatment of choice.[41] Acute extrapyramidal reactions are common and patients should be warned of the possibility of tremor, stiffness, and oculogyric crisis, all of which will respond to antiparkinsonian agents, for example procyclidine. Antiparkinsonian drugs should only be taken if these problems arise. Haloperidol can cause excessive sedation which has been termed a 'fog' state.[42] Sulpiride[28] and pimozide[43] can also cause extrapyramidal reactions but are less likely to and appear to have broadly similar efficacy.[44]

Because of reports of sudden death due to arrhythmias, pimozide is less used now. Prior ECG and subsequent monitoring is advisable and a response will have usually been achieved by 8 mg in a single daily dose if it is to occur.[43]

Phonic tics are usually the first to respond to drug treatment and then complex motor tics and then simple motor tics.

Tourette's syndrome may be associated with other psychopathology, particularly obsessive compulsive symptoms. Rhythmic complex movements that appear compulsive, for example, repetitive kissing or lining up are called complex tics in the American literature, but as they seem to lie between Tourette's syndrome and obsessive compulsive disorder, they are perhaps best referred to as complex movements. Sometimes these movements are the main problem. Neuroleptics usually leave them untouched but they will often respond to clomipramine where specific treatment is required.

Tics wax and wane but some children go into 'status tic', a sequence of unrelenting tics and complex movements that leaves them sore and exhausted. In the absence of a more specific remedy, chloral induced sleep will sometimes bring relief.

Clonidine has its advocates and has the advantage that it is not a neuroleptic but there are doubts about its efficacy[45] and in my hands it causes depression and does not affect the tics at all.

Naturally there are concerns about the lifetime risk of tardive dyskinesia in this new cohort of children receiving long term neuroleptics. Drug free days are advised once or twice a week, perhaps at weekends, to diminish the lifetime weight of drug consumed. Treatment alternatives under investigation include buspirone and calcium channel blockers.

Anxiety, panic attacks, and school refusal

Situational anxieties or phobias are best treated with behavioural methods. In school refusal in the younger child, anxieties are multifactorial and early return to school is the cornerstone of management. Anxiolytics have been used but results are conflicting as to their efficacy. Benzodiazepines are best avoided because of their addictive potential and propensity to behavioural side effects.

Free floating anxiety and panic attacks may be associated with hyperventilation which can be assessed in the clinic. Propranolol may be helpful but is contraindicated when there is a history of asthma or arrhythmia. It has the advantage that it can be taken 'as required'. The tricyclic drugs, amitriptyline and imipramine can be given for their anxiolytic effects. The present generation of monoamine oxidise inhibitors (MAOIs) is difficult to use because of the food restrictions required to avoid a pressor reaction. The newer reversible inhibitors of monoamine oxidase, for example, moclobemide may render this category of drugs more available to teenage patients.

Hysterical disorders and eating disorders

Hysterical and somatising disorders are included here because they are sometimes complicated by depression which should be diagnosed and treated in the usual way. Likewise, the depression sometimes found in chronic fatigue syndromes and anorexia nervosa. Abreaction with intravenous amylobarbitone[46] can be helpful in the management of psychogenic stupor, as it is difficult to gain therapeutic access to a patient who can neither move nor talk.[47]

There is no specific drug treatment for anorexia nervosa, but both imipramine and fluoxetine have found support in the treatment of bulimia nervosa.[48]

Elimination

The management of encopresis is not usually undertaken before age 4 years for developmenta reasons. Constipation is frequently associated and laxatives may be required. The choice of laxative is important, but 'sister's favourite' is often prescribed by default. The area has been reviewed recently by Graham Clayden and is not further discussed.[49]

Likewise, developmental considerations determine nocturnal enuresis is not usually treated actively before age 5 years. There is abundant evidence that behavioural methods are the treatment of choice after physical causes have been rejected. Some children respond to simple star charts rewarding dry nights.

Other children require a night trainer alarm that uses the same principle as the bell and pad and is equally effective but more convenient.[50] Many districts now have enuresis clinics to provide this service. Despite the above, amitriptyline and imipramine are still widely prescribed for nocturnal enuresis by general practitioners[1] and child psychiatrists.[2] Although effective in the short term, relapse is frequent when the drug is stopped and the risk of overdose by patient or siblings is well known.[3-]

There may be a place for prescribing one of these drugs in the short term, for example, to allow a child to go on a school holiday and the same can also be said for intranasal desmopressin,[51] but in the presence of safer, more effective behavioural methods the widespread use of drugs to treat nocturnal enuresis cannot be endorsed.

In daytime wetting, behavioural methods

including regular potting are the mainstay of treatment, but urodynamic review should be considered, particularly when there is associated urgency. Most of the drugs used by urodynamicists can provoke nightmares.

Hyperactivity

Children with pervasive short attention span and restless, overactive, distractable behaviour meet criteria for hyperkinetic disorder according to the *International Classification of Diseases,* 9th revision[52] and attention deficit disorder in the American system *Diagnostic and Statistical Manual of Mental Disorders,* 3rd revision revised.[53] Attention deficit disorder defines a much broader group as it also includes situational expression of these problems and it is not further discussed here.

Hyperkinetic disorder, narrowly defined, is of early onset and occurred at a rate of 17 per 1000 boys aged 6–8 years in the east London study.[54] British child psychiatrists are reluctant to make this diagnosis but usually identify the conduct disorder with which it is often associated.[55] Hyperkinetic syndrome is a handicapping condition. Management is difficult and requires attention to structure and consistency which usually involves environmental manipulation. Stimulant drugs are widely used in America; probably the best researched psychotropic drugs in use in childhood and scarcely used in Britain. Even if reserved for the most severely afflicted children who show this behaviour at home, at school, and in the doctor's office, every health district has candidate patients.

After diagnosis, baseline parent and teacher ratings using the Rutter[56] or Conners scales[57] are completed which takes a few minutes. These can be repeated serially to assess change. Methylphenidate[58] and dexamphetamine are both effective. A Yes-No effect is sought. When there is benefit it is clear and the school dinner lady will notice if a tablet is omitted. What is more, the child's improved behaviour is likely to have a positive effect on family interaction.[59]

Methylphenidate is only available in the UK on a named patient basis from the company (CIBA Laboratories, Horsham, West Sussex RH12 4AE). It has a short half life and it is given in divided doses in the range of 0·3–1·5 mg/kg/day starting with about 5 mg daily depending on the size of the child.[5] Appetite suppression is sometimes a problem so I usually give it after breakfast, after lunch, and maybe after school. Evening doses cause insomnia.

Reversible growth failure is reported and is probably related to high dose regimens. Nevertheless, height, weight, and blood pressure should be measured at each clinic attendance and this means the clinic should be equipped to do this. Drug 'holidays' are recommended for one or two days at weekends if this can be tolerated and for longer periods at least once a year. Some children become tearful or depressed and others may develop obsessive compulsive behaviour or tics. Tics are usually cited as a contraindication.[6]

Dexamphetamine is longer acting and may be given twice daily. The dose range is similar and so are the side effects. Some children tolerate one of these drugs more readily than the other. It is said that stimulants are ineffective in hyperactive children who are mentally handicapped, but a trial is still worthwhile in selected cases.[60] Although both dexamphetamine and methylphenidate are controlled drugs, dependence is not a problem with the doses described here. Low dose imipramine, 25–15 mg daily is a useful but less potent alternative.[61]

Behaviour problems in children with epilepsy

Children with epilepsy are at much greater risk of behaviour problems. The reasons for this are multiple but only drug issues are considered here.

It is profitable to review the anticonvulsants the child is taking. The behavioural side effects of carbamazepine are often associated with peak serum concentrations and a switch to the sustained release preparation at the same total daily dose is easy to do, will seldom result in decreased seizure control[62] or deteriorating behaviour, but sometimes produces a gratifying behavioural improvement.

The behavioural side effects of phenobarbitone are well known and paediatricians hardly use it, but some adult specialists who also treat children are unfamiliar with this side effect.

Clonazepam and clobazam can both cause profound and chronic behavioural deterioration, even pseudodementia, if parents do not decide to stop giving them. There is sometimes cross reactivity between the two compounds but sometimes not, so it is worthwhile to try a switch. Hyperactive children with learning difficulties and intractable seizures, who have been on a benzodiazepine from an early age, are particularly at risk that the drug induced behaviour will be assumed to be constitutional.[63]

Vigabatrin has made a notable contribution to childhood psychopathology and can produce a spectrum of problems including psychosis.

One is reluctant to treat anticonvulsant induced hyperactivity with stimulants. Dexamphetamine raises the seizure threshold and is recommended over methylphenidate, which is said to lower it, in the treatment of constitutionally hyperactive children with epilepsy. In practice methylphenidate may ameliorate or alter the seizure pattern in addition to its expected effect.

Behaviour problems in children who are mentally handicapped[7]

Mentally handicapped children who present with behaviour problems divide conveniently into two groups those who are on drugs and those who are not. Those who are on drugs are probably on too many and sometimes show the fluctuating symptoms of a subacute confusional state. Treatment comprises drug rationalisation and reduction in the shadow of tardive dyskinesia.

Children and teenagers who present with behaviour problems severe enough to warrant consideration of drug treatment will usually have self injurious behaviour or challenging behaviour if they do not have a more conventional diagnosis, for example, depression or bipolar disorder,[64] which should be treated appropriately. Sometimes there will be a more straightforward explanation, for example, toothache or departure of a familiar member of staff from a children's home.

Self injurious behaviour, for example, headbanging or eye gouging is very difficult to treat.[65] Naltrexone has been tried in recent years with some success.[4 66] Carbamazepine can also be used.[67] Challenging behaviour usually refers to explosive and aggressive behaviour in teenagers with limited language and limited responsiveness to social cues.

Management is expensive, person intensive and requires structure, continuity, and environmental manipulation. Regular exercise may also be of help.[68] Drugs may have a role but should always be assessed with a serial record of the frequency of the target behaviours against a baseline taken before the drug was started.

Neuroleptics should be avoided as far as possible because of the risk of tardive dyskinesia that can follow even a short period of neuroleptic treatment at low dose. Their short term efficacy is seductive. Dependent upon assessment of the problem, a separate exhibition of carbamazepine,[7 69 70] propranolol,[7 71] or lithium[6 7 72] may all be considered.

This world of chronic handicap is swept by enthusiasms. Fenfluramine has fallen out of favour for autism,[4 73] but amantadine and calcium channel blockers are on the horizon.[74]

It is always a serious decision to recommend parents give drugs to their children. Sometimes it is a serious omission not to recommend parents give drugs to their children.

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STATISTICS FROM THE INSIDE

8. Size, power, and confidence

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This note is intended to bring together and enlarge upon some of the points I have made earlier in the series on significance testing and estimation, as I have found that there are some misunderstandings that are quite widespread. At the risk of repetitiveness, let me begin by recalling the way that significance testing works. Suppose clinicians are considering doing a clinical trial of a drug treatment which is intended to increase forced expiratory volume in one second (FEV$_1$) in asthmatic children. Passing over many details that will be of importance in practice, they will start by contemplating a *null hypothesis,* in this case an assumption that the drug may have zero average effect (either absolutely or over and above that of a placebo) in a defined population of patients. From one viewpoint (not necessarily the most informative one) the trial may be regarded as providing an opportunity for the null hypothesis to be disproved.

When in due course the results of the trial become available and have to be interpreted, there are two kinds of mistaken conclusion that can be arrived at.

(1) The null hypothesis may be true, but it may be concluded that a real non-zero average treatment effect exists. In the jargon, the null hypothesis is *rejected* when it is actually true. This is a kind of false positive error and is known as an error of type I.

(2) The null hypothesis may be false—the treatment may have a true non-zero average effect—but the trial may fail to establish its falsity. Some statisticians would say that the null hypothesis was to be *accepted,* but this is unnecessary; a not proven verdict is enough. This is a kind of false negative error and is known as an error of type II.

Statistical significance testing is basically a methodology for controlling the rate of occurrence of type I errors. The null hypothesis asserts that the population mean effect of the treatment is zero, but almost certainly the sample mean effect will differ from zero in either a positive or negative direction—there will be a *discrepancy* between the sample mean and the hypothetical population mean. Statistical theory plus some suitable calculations enable the clinicians to assess the probability of getting, by chance alone, a discrepancy as large as the one that has actually been observed in the trial results. This probability is the *significance probability* of the trial data. If it is small (1 in 100, say), there are two possible explanations: (1) something very improbable may have occurred or (2) the null hypothesis (on the truth of which the calculation of the significance probability was based) may actually have been false.

If the significance probability is small enough, it will be natural to adopt the second of these explanations, thereby rejecting the null hypothesis. In actual fact, the null hypothesis may be true, and the decision to reject it may be mistaken; this is a type I error. The probability of making such an error is precisely the significance probability.

Suppose, though, that the significance probability of the observed discrepancy is not very small: 20–30%, say. The clinicians may then feel that they cannot reject the null hypothesis with an adequate degree of certainty. This does not of course mean that the null hypothesis is true; it may be false (the treatment may have a real non-zero average effect), and in this case a type II error will have occurred.

The clinicians considering the design of their trial will undoubtedly want to know the probability of making a type II error, and statistical theory will help to provide this. The calculation will require three pieces of information.

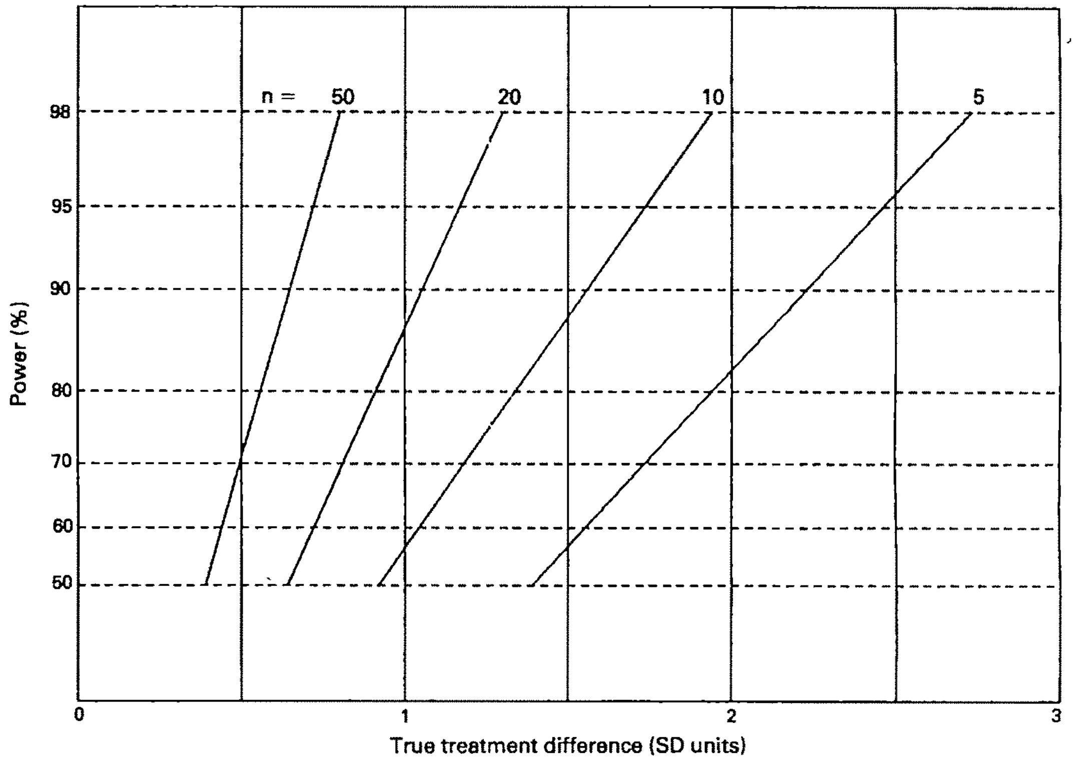
(1) The significance level demanded at or beyond which the null hypothesis will be rejected. This is called the *size* of the test and is usually denoted by α. The smaller the value of α (the greater the degree of protection against making a type I error), the larger is the probability of making a type II error.

(2) The precision of the sample estimate of the treatment effect. Note that this will depend upon the standard deviation of the observations and also upon the sample sizes. The worse the precision (the greater the standard deviation or the smaller the samples), the larger is the probability of a type II error.

(3) The true departure from the null hypothesis. The smaller the true departure (the smaller the true treatment effect), the larger the probability of a type II error.

The probability of making a type II error is usually denoted by β, and $(1-\beta)$ (the probability of *not* making a type II error) is called the *power* of the test.

It will be seen that the power is quite a complicated quantity. Let us, to save trouble and thought, follow convention by choosing $\alpha=0{\cdot}05$. To find the power we still need to specify both the true discrepancy away from the null hypothesis (that is, the size of the true treatment effect), and also the data precision. This latter will involve both the inherent variability of the material (which is measured by the standard deviation) and also the sample sizes. For any particular level of precision, we can calculate the power for a whole range of possible discrepancies and plot the results, obtaining in this way a *power curve.* A set of power curves is illustrated in the figure. These



Power curves for a trial comparing two independent samples of equal size, using an unpaired t test The parameter n is the number in each of the groups.

relate to an unpaired situation for the comparison of the mean of a treated group with that of an independent control group of equal size. The points to notice are: (1) there is a power curve for each value of *n*, the size of each of the samples, and (2) the discrepancy axis is graduated in standard deviation units.

A set of curves such as those in the figure enable the clinicians to make an instructed choice of sample size. Suppose for example that a true mean treatment effect equal to 1 standard deviation was of clinical importance and that the probability of missing such a difference—of failing to reach the 5% level of significance when the trial is performed—is to be at most 0·10 (a power of 90%). Then the figure shows that the number of patients in each group should be at least 25 or so. It also shows what power would be achieved by this sample size for other values of the discrepancy.

It will be seen again that there are three quantities to be specified before the above argument can be used: the size α, the power required $1-\beta$, and the discrepancy to be detected. What is more, the discrepancy must be expressed in standard deviation units—enough must be known about the subjects in the trial for a good guess at the standard deviation to be made.

Just as α is usually taken to be 0·05 (for no very good reason), so also values of β of 0·1 or even 0·2 are commonly used in designing a trial. The tacit implication is that it is more important to avoid recommending an ineffective treatment than it is to fail to spot one that is actually effective. It is not at all clear that such an attitude is always, or even commonly, appropriate.

It is of great importance to realise that the whole of the above discussion, including the concepts of size and power, has related to the stage of planning the trial, before any results have been obtained. Obviously the possibility of type II errors has to be taken very seriously later on when the results are to hand and have been analysed. However, the clinicians' position *vis-à-vis* the results is now different—they are known and their significance level is no longer subject to uncertainty. The interesting problem now is to specify what hypothetical situations might plausibly have given rise to the data. We no longer have to ask 'How large a true effect might we fail to detect in our proposed trial?'; instead the question becomes 'How large a treatment effect must we still consider plausible, now that our trial results are known?'. The concept of power is replaced by that of *confidence*. Suppose that the findings do not reach significance at some preagreed level; then the original null hypothesis is to that extent consistent with them and provides one possible explanation for them. But it is of course possible to go much farther than this. It is possible to work out a whole range of hypothetical true values of the treatment effect which are in this sense 'plausibly consistent' with the actual data. This range is a confidence interval for the true treatment effect. As well as indicating the range of 'plausible' hypotheses, the width of the interval incidentally provides evidence that the design of the trial has (or has not) been successful in achieving the anticipated level of precision. Notice that a mere report of the significance level achieved—let alone the bare statement that this level did or did not fall short of the magic 5%—is quite inadequate from both viewpoints.

It follows from the above discussion that considering the power of a proposed trial during the design phase is mandatory, for economic reasons and often for ethical reasons as well. It is inexcusable to embark upon an investigation, especially one involving animal or human subjects, which does not have a good chance of detecting an effect of the size which is considered important. This is why many statisticians demand that the power calculations made when designing the trial should be reported along with the trial results. But it must be emphasised that these calculations rank with assertions that the trial has been approved by the appropriate ethical committee, and are not of direct interest to the readers when they come to interpret the trial results. Their principal requirement at this stage will be a confidence interval for the true treatment effect, so that they can decide for themselves whether this effect may be large enough to be of practical importance in their own particular circumstances.

Confusion between power and confidence leads to difficulties when it is desired to establish a negative conclusion—say, that a treatment has a zero true effect in terms of some undesirable outcome. An argument which is sometimes put forward runs as follows:

(1) The trial was designed to have a small type II error rate β for a given level of significance α;

(2) The results of the trial were not in the event significant at level α;

(3) Therefore the null hypothesis of no real treatment effect can safely be accepted.

This argument fails to stand up for several reasons:

(1) The type II error rate β is the probability of failing to achieve significance for a particular non-zero size of treatment effect. At best, only the absence of an effect of this size could be asserted.

(2) The power calculations were based upon assumptions about the underlying variability of the data, which had yet to be obtained. These assumptions may not have been met—the data all too often turn out to be more variable than had been expected.

(3) The design type II error rate may have been as high as 0·1 or 0·2. Again at best, the desired assertion could only be made with this limited degree of certainty.

As I have explained, the consideration of a confidence interval for the true treatment effect makes an approach of this kind unnecessary. The appropriate confidence limit shows the size of the largest true treatment effect that is plausibly consistent with the data. Only if this limit is close to zero can the absence of an appreciable real treatment effect be confidently asserted.

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CURRENT TOPICS

The ethics of cardiopulmonary resuscitation. I. Background to decision making

J M Davies, B M Reynolds

The ethics of cardiopulmonary resuscitation (CPR) have been closely studied in adults where there has been wide experience.[1–17] Children and babies have been less well studied.[18–26] Most successful CPR of adults occurs in primary cardiac arrest, whereas paediatric and neonatal cardiac arrests are usually secondary to disturbance in other systems, and the child's heart can often be revived long after the brain is irreparably dead. Is extrapolation from work on adults to medical practice with infants feasible or desirable?

'Everyone who dies suffers a cardiac arrest',[16] the last stage in the process of dying.[1,12] Prompt CPR from bystanders[4] or professionals[25] may be beneficial for some, but in other cases may be futile,[10] harmful,[11] and cruel.[6] CPR frequently prolongs dying,[5,6,11] and occasionally results in a persistent vegetative state as the heart is more tolerant than the brain of hypoxia.[5,6] Indeed Youngner stated that 'CPR is so invasive and potentially damaging that it symbolises the worst excesses of medical technology'.[12] We have observed that CPR may be so distressing that parents frequently leave the room when their child is dying or being confirmed as dead by failed CPR.

Choices

Hospital death rates greatly exceed CPR rates,[2,5] so choices are being made but paediatric statistics are not widely available.

The apparent choice between CPR and 'do not resuscitate' orders is a 'chance for life versus certain death'[6] but the true choice may be between prolonged,[5,11] 'multiple invasive, painful and dehumanising procedures'[6] versus a dignified death in familiar surroundings and company, with adequate analgesia.

Those 'choosing' CPR may often be choosing something that does not exist—the chance for the patient to live.[6] CPR has to be started immediately[4] so any decisions must be prospective, but inappropriate use may be inevitable in many situations.[1,5,11]

By using simple arithmetical formulas and clinical examples[13] medical decision making has been analysed from the medical and economic viewpoint balancing the uncertainties of aggressive potentially life sustaining treatment and the greater certainties of supportive treatment. Paediatric and neonatal practice cannot escape choices resting on this balance between needs, outcomes, preferences, and resources. Further research is required regarding outcomes in specific subgroups as well as consensus studies of informed preferences of these subpopulations.

Prediction in critically ill adults[27] has been very accurate regarding death and fairly accurate for 'awakening' after out of hospital cardiac arrest.[28] Predictions of death in very low birthweight infants have also been studied and used in comparisons of medical performance.[29]

Medical and surgical complications of CPR

All degrees of brain injury, cardiac complications (in particular heart failure, hypotension, and arrhythmias), thoracic and mediastinal injuries, bone marrow emboli, renal failure,[30] and gastric rupture[31] are described in adults. Retinal haemorrhages are well recognised features of non-accidental injury (NAI) in children,[32] yet they may be a consequence of CPR,[33,34] though some claims have been doubted.[35]

Inadvertent rib fractures may occur in successful CPR, but we have seen an infant whose parents alleged that old bruising and even older rib fractures were caused by their own resuscitation attempts which had not come to medical attention; most such fractures are due to NAI not CPR.[36] We have also seen oesophageal rupture due to NAI blamed on subsequent CPR: a potential for diagnostic and legal enigmas. Many paediatricians will have seen the consequence of pulmonary air leaks and pharyngeal or laryngeal trauma after CPR.

Risks of transmission of HIV

There is no evidence that contact with saliva,[37] or mouth-to-mouth resuscitation,[38–40] has resulted in HIV infection; but most mouth-to-mouth resuscitation is given to familiars,[39] and 'zero numerator does not necessarily mean no risk'.[41] HIV transmission by needlestick injury is well recognised.[39] There is an increased risk of HIV transmission in emergency departments[42] and to health workers,[43,44] but studies from San Francisco have not so far indicated a decline in bystander CPR or lay training.[39] The balance of probabilities in the case of an unknown victim favours the safety of CPR[40]; this must particularly apply to bystander mouth-to-mouth resuscitation of children in the UK at present.

Brain resuscitation

The outcome of CPR is governed partly by the pre-existing status and partly by the effects of

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the arrest on the brain, ranging from death,[30] brain death,[45] persistent vegetative state,[46] handicapped survival,[25] or intact survival.[30]

The aims of treatment are to provide rapid effective CPR, the control of brain swelling and fits, and the maintenance of normal homoeostasis. Much neuronal injury and death occurs after circulation has been restored, so research into the use of calcium antagonists, phenytoin, prostacyclins, free radical antagonists, and amino acid antagonists is proceeding. Current views suggest that it is premature to incorporate these experimental measures into clinical practice.[47–51] Success with these drugs would tilt the balance towards CPR in the case of previously normal individuals who have suffered from delays in effective CPR.

The concept of futility

The concept of futility is well reviewed in adult practice.[3,6,8,10–17] Providing CPR for a patient with absolutely no chance of success is clearly futile, but the concept can be extended to cases with a probability of survival greater than, though approaching, zero[8,10,16] as it recognises the rarity of exact prediction[6,10,11] and the counterbalancing medical costs to the patient.[10,11,13] The concept involves investigation of, and respect for, achievable goals of the patient and family[3,8,10,11,14] but excludes financial or resource considerations and choices between patients.[10]

Apart from medical judgments there are at least three other near imperatives involved in making decisions not to resuscitate: patient or family autonomy, legal and judicial opinion and local, temporal, or universal availability of scarce medical resources.

Medical futility versus patient autonomy

There are limits to a doctor's obligation to meet a patient's request for specific interventions and the risk of a 'slippery slope' of inappropriate requests. There needs to be 'a modicum of potential benefit as seen from the medical perspective'.[52] Although Brett and McCullough did not specifically discuss CPR, their analysis and guidelines have become a benchmark for dealing with aspects of this problem in adult[6,8,10,15,16,53] and paediatric practice.[54]

Patients may suffer when autonomy overrules the medical judgments of the futility of CPR[3,6,11] and these differences of opinion require further discussion to reconcile realistic goals of the doctor and patient or family, as there may be a trade off between quantity and quality of survival.[55]

Patients and families who are offered treatment are not accustomed to turning it down and usually assume there must be benefit.[6,11] Therefore futile CPR should not be provided as a 'high technology placebo' in hopeless cases,[6] it should not even be offered,[6,10,11] though there should be full discussions,[3,12] which must be sensitive[16] and realistic,[14–16] so better forms of communication and management may be required.

There is a need for informed consent and autonomy when true choices exist and an effective social dialogue to ensure a shared understanding of 'what counts as a reasonable chance for worthwhile benefit relative to an acceptable risk of harm'.[10]

Legal aspects

After the death of baby Jane Doe in Bloomington, Indiana in 1982, new legislation and bureaucracy was introduced in the USA to ensure that all newborns receive maximal life saving treatment except where there is irreversible coma, where death would merely be delayed, or where such treatment would be futile or inhumane. Baby Doe's parents, with the concurrence of her physicians, had refused consent for possibly life saving alimentary tract surgery on the grounds of handicap by Down's syndrome.

The legislation has been well reviewed from both the legal[56] and medical[21] angles, with significant reservations about the effects and design of the laws, though no actual cases are quoted.

Withdrawal of CPR might diminish potential or actual extension to life, but should not inevitably be opposed by the courts or jeopardise the physician responsible for good well documented medical care and judgments,[7,57] and this opinion was upheld in the case of baby L whose doctors refused in court to continue futile treatment with repeated CPR after profound acquired brain damage. Restraint may sometimes be advisable in the face of parental request to 'do everything possible'.[54]

Conversely a Grand Jury indicted for manslaughter the parents of a child who died after they refused bowel surgery in favour of faith healing.[58]

Consultant paediatrician, Leonard Arthur, was charged with, but acquitted of murder after prescribing dihydrocodeine before the death of a British baby with Down's syndrome.[59,60] In another case the Court of Appeal ordered life saving surgery in 1981 after the parents had refused treatment for their baby with Down's syndrome.[19]

A doctor in Scotland in 1987 was accused of failure to provide CPR in the case of a neonate that he considered was not viable because of extreme prematurity.[61] He was acquitted but admonished for poor communication.

In the case of a multiply handicapped ward of court, baby J, who had undergone repeated CPR, the Court of Appeal in 1990 ruled that 'the court is entitled in the best interests of the child to say that deliberate steps should not be taken artificially to prolong its miserable life span' and there should be no absolute rule 'to preserve life at all costs', but they should not set down 'an all-embracing test since the circumstances of these tragic cases are infinitely various' so that 'the issue in these cases is not a right to impose death but a right to choose a course of action which will fail to avert death'.[62]

Scottish, English, and American law all differ, but British courts should make decisions in medical cases on the basis of medical evidence with the intent of supporting good medical practice. Unfortunately, bad legislation is more often the consequence of difficult cases, pressure groups, and party politics.

Except where the infant is a ward of court, going to court ought to be the last resort, because courts are not the appropriate place to resolve the agonising problems that underlie the 'right to die' cases.[57] The clumsy involvement of the judiciary and legislature in 'distant ethics' of difficult paediatric and neonatal problems is due to the failure of paediatricians to grapple with 'close up ethics' of individual professional relationships with distraught parents.[23]

The American Medical Association in April 1991 published guidelines regarding the use of do not resuscitate orders, but did not consider children or the role of parents.[15] However, the Critical Care Society has recently spelled out its views on withdrawing life support in the critically ill, with particular reference to paediatric problems.[14] They recognise parental pre-eminence in decision making with a commensurate role for the older child,[22] but reject the full application of the baby Doe regulations as being ethically unjustified.

On 1 December 1991 the Patient Self Determination Act came in to force in the USA.[63–65] This defines the status of, and requirement for, advance directives with regard to life sustaining therapies including CPR. Both concern[63] and cautious welcome[65] have been expressed, but the effects on paediatric practice may be marginal.

Where there is time, decisions regarding prolongation of dying should preferably be taken by senior doctors[18 19 24 66] acting within the law after appropriate discussions and consultations in individual cases, rather than by the courts. Each decision must be documented and notified and communicated to any staff attending a cardiopulmonary arrest. It is unfortunate that the parliamentary health service commissioner has needed to become involved in the problem of CPR in hospital,[67 68] which is essentially a medical response to medical indications.

Summary

Futile cardiopulmonary resuscitation (CPR) may prevent humane care of the dying child and deprive parents of the opportunity to express their love, grief, and dedication at a critical moment, while appropriate and successful CPR may restore intact their child. Attempted resuscitation of corpses or children with terminal illness indicates inadequate knowledge, discrimination, and decision making. CPR is a medical procedure applicable to certain medical problems; weighing up the risks and benefits in each individual case is a medical function that is constrained by the law and must take full note of patient and family preferences, but cannot be governed by them and should not be over-ruled by laws based on complex but different cases. Time limits on occasions may curtail the full process of consultation and decision making. Applications of skills and resources in the right time and place requires understanding of the medical logistics and study of the potential for good outcome.

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The ethics of cardiopulmonary resuscitation. II. Medical logistics and the potential for good response

J M Davies, B M Reynolds

Cardiopulmonary arrest in a child or infant with a good capacity to respond needs to be matched by the timely availability of appropriate personnel and facilities. The provision of finance, adequacy of skill levels, hours worked, and sites covered by young doctors and the simultaneous demands made on staff in an emergency may all impinge on the availability of cardiopulmonary resuscitation (CPR) in hospital. Bystander CPR[1] and general practitioner[2] and paramedic services[3] may also be relevant, while studies of outcomes in specific subgroups of children may enable better targeting of resources.

Economic aspects

Medical resources will inevitably continue to decrease in relation to demand and need[4,5] so allocation and rationing is unavoidable.[6] Yet $16 million was awarded to a patient in Florida who sustained brain damage while nurses in a ward short of staff were busy attending to three other patients.[7]

A considerable excess of nocturnal perinatal mortality, noted in Lausanne in 1986, was partly attributed to reduced staff numbers, deterioration in medical functioning, and difficulty in organising resuscitation services at night.[8] Mildred Stahlman pointed out ironically that 'the cheapest baby is a dead baby and the quicker the cheaper if death is inevitable'.[9]

Skilled medical availability

The availability of skilled paediatric staff varies considerably in different districts and regions of the UK.[10-12] Some maternity hospitals have tiers of resident paediatricians, some with several years' experience in the specialty,[10,11] while others rely on general practitioner (GP) trainees on six month contracts with no previous experience to provide on site neonatal resuscitation.[10,13] Many of these GP trainees work a one in three rota out of hours and many are supervised by consultants who are not on site 24 hours per day 365 days per year[10,11,13]; many simultaneously cover emergency departments, children's wards and baby units, being on call up to 80 to 100 hours per week and with continuous spells of duty of up to 80 hours. Many consultant paediatricians still work in units with inadequate intermediate staff and make frequent out of hours calls to assist junior staff.[14]

A total of 19% of hospitals surveyed in Canada in 1987 had to summon help from outside the hospital if neonatal resuscitation was required.[15]

Recommended requirements for neonatal resuscitation services include someone skilled in neonatal resuscitation being present at every delivery,[16] or always in the maternity unit,[17] or the doctor responsible for resuscitation being accompanied by a doctor skilled in resuscitation until competence is achieved,[18] or a doctor skilled in resuscitation present at all 'high risk' deliveries.[19] Applying such a criterion[19] to a review of deliveries at a district general hospital in Sheffield[20] in 1984 would have required an 'advanced resuscitator of the newborn'[17] to attend about 40% of all deliveries, though well under 1% of term infants had an Apgar score of 3 or less.

Surveys, of British house officers' skills[21-23] and retention of skills,[24] have consistently shown inadequacy at CPR. Surveys of 'office pediatricians' in the USA have shown inadequacies in relation to paediatric CPR.[2,25,26] Similar surveys of training and equipment for American paramedics showed deficiencies in relation to children.[3]

Two hundred and one out of 367 British GP trainees felt incompetent to intubate a baby after 6 months' obstetric training[27] and another assessment of their training in paediatrics made no reference to resuscitation skills[28]; indeed the relevance to general practice of experience in neonatal and much hospital paediatric practice has been questioned.[29]

There may now be too few babies requiring intubation in many sizable maternity units to allow useful house officer experience to be gained if the more difficult intubations which need a very skilled operator are excluded,[13] so that away from university centres doctors skilled in newborn resuscitation may be a relatively scarce resource in the UK in hospitals where middle grade staff are not employed.[10,11,13] For example, there were 3111 deliveries in Grimsby Maternity Hospital in 1990 and a consultant paediatrician, in general, attended deliveries of babies 32 weeks' gestation or less where skilled intubation is frequently needed. Yet during a six month period only six other babies required intubation, nowhere near enough for four inexperienced house officers to become adept even by the end of their six months. In theory, however, they were liable to be predictably called for between 1000 and 1200 deliveries per annum at all times of day or night, in addition to calls to unpredictable problems. Imbalances in paediatric staffing in the UK ensure that a substantial number of babies may not have access to instant skilled resuscitation, which may have tragic and expensive consequences. Midwives or neonatal nurses who usually stay longer in post than most young doctors may be a better

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source of skilled resuscitators,[13,15,30,31] but it may be necessary to reward those nurses with the skills.

Withholding CPR in neonates

There is consensus that withdrawal of intensive care and CPR may be considered in selected neonates[32–35] due to specific congenital malformations,[36,37] in infants with severe brain damage[38] and extreme prematurity[39]; other justifications have included renal necrosis, bronchopulmonary dysplasia, and failure to respond.[34] Ethics committees[32] and recourse to the law[33,35] are not recommended by British paediatricians to solve these problems, but 'compassion, humility and courage' are required by the doctor.[32]

Whitelaw considered 'near certainty of death' or 'no meaningful life'[35] as criteria for non-treatment and had he been able to predict the outcome in some of the worst of his multiply handicapped survivors he would have advised non-treatment. Such decisions must stand up to the most rigorous scrutiny[33] and Dunn said he would take the initiative in advising non-treatment, but if the parents disagreed after full discussion, he would continue full support.[32]

Failure to establish respiration by 20[40,41] to 30[42] minutes of age is usually a bleak sign after birth asphyxia and may be considered an indication for cessation of treatment.[40,42] There are many major uncertainties, however, regarding neurological prediction in newborn care.[43–45]

Modern methods of brain investigation including evoked responses,[46] computed tomography,[47] radionuclide imaging,[48] cerebral blood flow Doppler studies,[49] magnetic resonance spectroscopy,[50] intracranial pressure monitoring,[51] and two dimensional ultrasound[52] have increased our knowledge of pathological anatomy and physiology and may allow outcome predictions with varying degrees of reliability, particularly in the worst cases.

Withdrawal of treatment due to extreme prematurity must depend on the prospect of a successful outcome for the given maturity and pathology of the baby, in that unit or elsewhere. There is evidence that different units have different definitions of live birth as opposed to abortion at very low gestation,[53–55] so that not only is initial assignment for possible treatment variable but statistics may be distorted[56]: there seems to be a secular trend in these respects.[57,58] Recording total perinatal wastage might address this problem.[59] At present, obstetricians may try to ensure that pregnancies with a potentially good outcome deliver in the labour wards and allow abortions to occur in the gynaecology wards,[56] where CPR is not routine, so their decisions have a major impact on viability.

CPR in the labour wards

Significant birth asphyxia may manifest as Apgar scores 0 to 3. Babies with an Apgar score of 4 or more should, in most cases, respond to basic CPR, whereas those with an Apgar score of 1 to 3 often require intubation for a good result. An infant with Apgar score of 0 if not resuscitated becomes a fresh stillbirth with no handicap. Review of resuscitation of 126 babies with an Apgar score of 0 showed 48 survivors but only 24 were normal at follow up and nine had severe handicap,[40,42,60,61] so resuscitators must appreciate that treating babies with an Apgar score of 0 has definite risks.

CPR in the neonatal intensive care unit

Two large series reporting the outcome of CPR in a neonatal intensive care unit showed 11 survivors, out of 133 infants, with four apparently normal.[62,63] Cardiac arrest is usually a terminal event in very low birthweight infants receiving full intensive care and CPR may be considered futile unless the arrest is very brief or associated with a blocked or misplaced endotracheal tube or the need for intubation.[63]

Failure of CPR or decisions to terminate treatment may result in varying combinations of bereavement, guilt, and anger. As well as the short term anguish, long term psychological distress is quite common but can be minimised by various strategies which have been well reviewed recently.[64,65]

Paediatric CPR

Apart from very rare acute arrhythmias, cardiac arrest is usually terminal in children and where possible better prevented than treated. Certain severe conditions may herald incipient prearrest such as acute epiglottitis, obstructed airways, severe hypovolaemia, diabetic coma or adrenal crisis, tension pneumothorax, haemopericardium, and anaesthetic mishaps.

Prompt treatment of the primary cause plus pulmonary and circulatory resuscitation may abort a cardiac arrest, but once it occurs the prognosis is frequently grim,[66–68] and not much improved by transfer to hospital,[67–69] though acute respiratory problems such as smoke inhalation, drowning,[69,70] and choking may respond well to expeditious and competent CPR.[66,68] In hospital the outcome for respiratory arrest is better than for cardiopulmonary arrest.[71,72] Where cardiac arrest occurs, despite increasing supportive care, the outcome is usually proportionately poor,[73] and a poor outcome is likelier with prolonged or delayed CPR[66] and the need for drug treatment.[1,72,74]

Paediatric drowning

Review of four series of children brought to emergency departments apnoeic and pulseless after drowning showed 20 dead children, 20 severely damaged, and no intact survivors.[1,67,75,76] In contrast, bystander CPR was followed by 19 deaths, 23 cases of brain damage, and 88 intact survivors out of 130 children. Bystander CPR may be unnecessary in milder cases, is more timely in more serious cases, and acts as a triage in the worst cases. Twenty of the 23 children with severe brain damage were in fact resuscitated in hospital, though occasionally remarkable survival is described,[70] and CPR should not be abandoned in nearly drowned children until they have been rewarmed.[77]

More research is needed into preventing immersion, parental training in CPR for those at risk, and the medical management of drowning.[78]

Near-miss sudden infant death syndrome

The risk of sudden infant death syndrome (SIDS) is greater after near-miss SIDS[79] and hospital admission is indicated.[80] Parents should be provided with a monitor, taught CPR and given support,[81] although SIDS continues to occur in the face of these measures.[82] It may be possible to identify subgroups at particular risk.[83]

Cardiac arrhythmias

The long QT syndrome may be lethal,[84] is rare,[85] but may respond well to electrical treatment,[86] drugs,[86 87] or surgery.[88 89] Other causes of serious ventricular arrhythmias and cardiac arrest in children include drugs[69 90] and cardiac tumours.[38] Although these arrhythmias are rare, doctors need to be aware of the possibility of, and means to achieve, a good prognosis and parents of children at risk should be taught CPR.[91]

Summary

Mismatches between provision of paediatric cardiopulmonary resuscitation (CPR) and potential to benefit are examined. Deficiencies are most likely to occur in peripheral maternity units but futile CPR is more common in emergency departments where the child is unknown. Decision making in individual cases is best retained by the medical profession for the sake of the child and family. American style intervention by the legislature is likely to dissipate scarce resources and perhaps harm infants not capable of benefiting.

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Suitability of the paediatric setting for hospitalised adolescents

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As maturation cannot always be related directly to chronological age, the parameters of adolescence are difficult to define. In general terms, the period 10–20 years provides useful boundaries and incorporates the transitions from childhood to adolescence and adolescence to adulthood. Adolescence is a relatively healthy time compared with other age periods, but although morbidity and mortality are low, young people present a wide range of medical and surgical disorders, psychiatric disturbance, sexually related problems, and the consequences of risk taking behaviour. While their health needs are met principally at primary care level, adolescents requiring medical and surgical care in hospital present complex and controversial problems. Worldwide, there is still limited recognition of the special health care needs of this age group, although there are increasing numbers of children with chronic or life threatening diseases surviving into adolescence.[1] In addition, although the demographic trend in western society suggests that the numbers of children and adolescents will fall,[2] there is likely to be growing recogntion of the social and economic importance of the health of teenagers.

Very few all adolescent units and associated services have been set up in the UK, with the exception of those within the psychiatric service, established regionally since the late 1960s.[3] Generally, adolescents continue to be nursed with either adults or children, and both settings may provide unsuitable facilities. In this respect, a succession of recommendations, made over the last 30 years,[4–7] has been largely ignored, despite the considerable number of adolescent admissions. In Glasgow, for example, inpatient admissions aged 12–20 years, in 1988, represented 12% of the estimated adolescent population of the Greater Glasgow Health Board area.[8] Those admitted to the Royal Hospital for Sick Children (RHSC) comprised 8% of the total admissions, increasing slightly to 9% in 1990.[9] Similarly, 9% of admissions to general hospitals in 1990 were adolescents (information from the Management Information Services Unit, Stobhill General Hospital, Greater Glasgow Health Board, 1990).

The general failure to implement recommendations for improving adolescent health care and the increasing numbers of hospitalised adolescents provided the impetus for a descriptive study (1990), in Glasgow, of the psychological, social, and environmental needs of adolescent inpatients at RHSC.[1] The findings, which provide empirical evidence of the continuing need to improve adolescent health care, constitute the framework of this review. Additionally, consideration is given to the underlying reasons for delay in supporting change.

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Review of recommendations

Recognition of the need for change in adolescent health care has been expressed for many years, commencing in 1959, with the Platt report.[4] Recommendations included, for example, the desirability of separate accommodation for adolescents, and the suggestion that teenagers should not be able to overhear potentially upsetting adult patient conversations. In 1976, the Court report recommended that staff caring for adolescents should have enhanced training to help them meet young people's needs, although special care was regarded as unnecessary.[9] Adolescents' educational needs have also been considered,[10 11] although Warnock pointed out that education is a 'right' and is 'desirable' in hospital, but is not a legal requirement.[12]

In 1985, the British Paediatric Association made detailed recommendations concerning accommodation, education, and transfer to adult services, while also pointing out some of the problems inherent in nursing adolescents with either adults or children.[6] It was suggested that a special ward for teenagers would be beneficial because their developmental needs were of greater importance than their 'system specialty' disorders. Issues such as the need for privacy were addressed, as were facilities for recreation and education, including suggestions that there should be rooms where youngsters could be noisy or quiet. It was argued that transfer to adult services should involve consideration of levels of maturity, the wishes of the youngster and local arrangements, rather than rely simply on age. The unsuitability of paediatric wards was discussed, highlighting the potential feelings of frustration and embarrassment felt by adolescents who were nursed with children. Adult wards were regarded as equally unsuitable for teenagers, whose anticipated 'childish' behaviour was likely to be unacceptable to many adults, and, in particular, being nursed with adults with degenerative diseases was considered inappropriate.

The World Health Organisation has contributed to the recommendations about adolescent care.[5 13] In 1986, for example, it suggested that adolescents might be uncomfortable with staff used to dealing with children and that, generally, adult wards were insensitive settings for this group.[5] Special training for staff working with adolescents was advocated, because it was felt that the communication skills and attitudes of this staff group were of crucial importance. Several professional bodies, including the Royal College of Nursing,[14 15] supported the concept of separate wards for adolescents, set apart from those for adults or children. More recently, the National Association for the Welfare of Children in Hospital[15] (renamed 'Action for Children' in 1991) made explicit recommendations for the hospital care of adolescents and these are supported by the Department of Health.[16]

There appear to be several reasons for the failure to implement many of the recommendations. Firstly, inadequate staff training, concerning the special needs of both healthy and sick adolescents, stands out as an issue of overriding importance and means that teenagers are not acknowledged fully as a distinctive patient group.[17–21] Although their medical needs are met, there has been a widespread failure to develop services and expertise for their psychological welfare.[22] The fact that only a small number of adolescent wards has been established,[23] outside psychiatry, has contributed significantly to the relative unavailability of opportunities for theoretical and practical training.

A second group of reasons concerns change in the pattern of care delivery and all the implications of acknowledging another category of patients. This would involve, in particular, additional funding requirements and generate uncertainty about optimum staff deployment. The establishment of separate accommodation, for example, could result in the reduction of patient numbers in other wards, with the possibility of consequent staff reallocation depending on their interest in adolescent health. Attitudes towards adolescents as a group can often be negative and if a perceived threat, such as the transfer of patients from one ward to another, is added, it would not be surprising if medical and nursing staff lacked motivation for change. Further, the introduction and implementation of new training programmes could incur significant financial and manpower consequences.

Despite the plethora of recommendations, there has been little systematic research providing evidence about the merits of special services for adolescents. It may have to be accepted that many of the more costly recommendations will not be implemented until it is demonstrated that meeting the emotional and social needs of hospitalised adolescents actually enhances their medical outcome, as well as reducing expenditure. However, there is a growing body of medical and nursing staff who are interested in adolescent health, and it is possible that the opportunities for service reappraisal, associated with NHS reform, may create the climate for innovative change.

Shortcomings and solutions in a paediatric setting

Although the findings of the RHSC study cannot be generalised, it is likely that some or all of the shortcomings may occur in other paediatric settings. The solutions to the problems have different resource implications and are grouped accordingly. The present review is not concerned with the quality of technical nursing and medical treatment.

MINOR RESOURCE IMPLICTIONS

Many deficiencies are likely to be remediable using minimal resources, and should be considered even if funding is insufficient for more far reaching modifications.

Guidelines for adolescent patients

Adolescents are often unsure of what they are allowed to do in hospital and may be reprimanded for what they regard as normal behaviour.[1] In this context, printed guidelines or 'house rules', setting out the limits for acceptable behaviour, would be beneficial.

In-service training

In general, paediatric staff are not kept up to date specifically with progress in adolescent health care. In-service training provides a valuable medium for this purpose and could take the form, for example, of a regular multidisciplinary forum.

Communication

Some paediatric staff and adolescents experience difficulty talking openly and comfortably to each other; for example, teenagers often resent being spoken to as if they are either adults or children.[1] Such difficulties may perpetuate unresolved adolescent worries about being unwell or suffering pain.[1] It is essential, therefore, that staff dealing with adolescents should be trained to communicate effectively with them.[24] Adolescents have a right to be considered and responded to according to their maturational stage, thereby fostering the mutual trust that forms the basis of a therapeutic relationship.[25]

Recognition of social and recreational needs

Boredom can be a major problem for hospitalised adolescents, particularly those with chronic conditions,[1] and activities in children's wards are likely to be considered inappropriate. Peer company is essential, but is often lacking, especially in children's hospitals, because adolescents tend to be scattered in small numbers throughout the specialist wards.[1] A centrally arranged youth group can provide a valuable opportunity for teenagers to meet, providing the nursing staff are well informed about its existence and function.[1]

Independence

Adolescents may be restricted unnecessarily by hospital policies geared appropriately for children. Public telephones, for example, may be inaccessible because they are outside the wards, which patients are not allowed to leave unaccompanied.[1] This limitation may increase the sense of isolation often experienced in hospital,[26] yet could be easily remedied, for example, by the installation of mobile telephones.

Privacy

Every patient has the right to privacy, but this may tend to be neglected when adolescents are nursed with children.[illegible] In the absence of an adolescent ward with appropriate structural provision for privacy, teenagers should be accommodated in individual cubicles. Although one of the main functions of a cubicle is to accommodate resident parents, under some circumstances, adolescents' needs may be paramount.[illegible] Even when this is not possible, privacy during washing and bathing, or during medical examination, should be maintained scrupulously by the use of adequate screening.

Consent

Staff used to dealing with children or with adults may lack awareness of adolescents' precise legal rights when considering consent to treatment.[1] Adolescents have the right to consent, if considered mature enough to understand the implications of intervention, but in practice, it is usually the parents who are asked to agree to treatment and adolescents are rarely involved in the process.

MODERATE RESOURCE IMPLICATIONS

Hospital policies

Policies set for children, concerned for example with restrictions on television viewing, may be quite inappropriate for adolescents[1] and need radical reappraisal and appropriate modification. However, some decisions can be controversial; for example, although ward kitchens are appropriately out of bounds to children, there may be mixed feelings among paediatric staff about unsupervised adolescent access to these areas, until appropriate safety provisions have been introduced.

Medicine administration

Many hospitalised youngsters have chronic conditions requiring regular medication, for which they may have assumed considerable responsibility at home, although this is denied them in hospital.[1] Such inconsistency in expectations of responsibility and independence can be confusing at this impressionable stage, so modification in the current regulations covering medicine administration should be considered, encouraging self care by giving selected teenagers some responsibility for self medication in hospital. Nevertheless, despite possible psychological and economic advantages,[23] this would require difficult decisions concerning policy change at both hospital and health board levels.

Noisy and quiet facilities

Limited recreational accommodation in most paediatric wards can result in adolescents being told to make less noise or having no opportunity to be alone. Whether in a separate ward or with children, adolescents need space for their own activities, and every effort should be made to create such facilities.

Education

The importance of continuing education and the lack of appropriate educational facilities are not always recognised by paediatric staff, although both issues are likely to cause concern for teenagers and parents.[illegible] Education is vital for hospitalised adolescents and although difficulties exist, for example teaching small numbers in separate wards, these could be overcome by grouping all adolescents together whenever possible.

MAJOR RESOURCE IMPLICATIONS

Major changes will have serious implications in terms of funding, manpower, staff deployment, and structural change.

Professional training

Health care professionals of all disciplines are likely to have limited awareness of the psychological and social needs of hospitalised adolescents. Consequently, they are unable to recognise and meet their requirements.[19 20 22 27 28] Basic training should incorporate a thorough understanding of the maturational needs and problems of healthy and sick adolescents.

Adolescent wards

The accumulated evidence suggests that adolescents dispersed in adult and paediatric wards may be disadvantaged.[4 6 7 15 16–] A strong case can be made, therefore, for them to be accommodated in purpose designed wards, away from younger children or adults, with day to day care provided by nurses with specialised adolescent training. Locally devised policies would determine whether all or selected adolescents could be admitted to such wards. Many benefits could be derived from such a development.[1] Staff training could be implemented and enhanced, ensuring a nucleus of staff with the specialised knowledge required to care for adolescents. Independence and self care could be promoted and maintained; there would always be peer company and education would be facilitated. However, potential difficulties include the implications of combining patients requiring specialised nursing skills and the concentration of mentally disordered, non-compliant, or seriously ill patients. An overriding adverse perception may be that adolescents are more difficult to control as a group than they are in smaller numbers.[illegible]

Transfer to adult services

The inevitable transfer of adolescents from paediatric to adult services is a complex and potentially stressful issue, raising important questions about its optimal timing and management. Preliminary discussions with adolescents and their parents could help to bridge the professional gap between paediatric and general medical services. This should be initiated more than one year before transfer is due in order to assist the youngster and family in coming to terms with the enforced break with familiar staff and environment and to influence any preconceived doubts about adult wards.

Joint clinics between paediatricians and medical staff from general hospitals need to be established in most specialties, gradually introducing new personnel and explaining the necessity for change. However, the geographical locations of some hospitals and existing commitments of senior medical staff involved are likely to necessitate considerable reorganisation.

Conclusion

There are undoubted deficiencies in the provision of the optimum hospital setting for adolescents. Although it is customary to highlight the adverse effects of care in adult wards, research referred to in this review indicates that the paediatric setting is also not immune from criticism. Difficulties can be identified readily and many defects that impair the experience of adolescent hospitalisation are rectifiable without major funding.

At a time when holistic patient care is at the centre of NHS reforms, the psychological and social aspects of the medical and nursing care of adolescents in children's wards and hospitals can no longer be neglected. There is no justification for managers, educationalists, and practitioners of all disciplines, working in paediatric settings, to overlook the shortcomings of staff training or the adverse effects of environmental deficiencies and outmoded operational policies on the quality of adolescent health care. While it could be argued that a comfortable, age appropriate environment with peer company will not necessarily have a direct influence on medical outcome, there is little research evidence on this issue. Nevertheless, there are some indicators of benefits—for example, facilitating pain relief by reducing anxiety caused by noise or lack of privacy.[29 30] This illustrates the way environment and appropriate accommodation may have direct impact on actual medical outcome, with the added benefit of reduced costs, resulting from shortened stay.

While full acceptance of the necessity for major change may await evidence of the benefits in economic terms, fundamental decisions have to be made about the proper locus of responsibility for the care of hospitalised adolescents. The current climate of change in the NHS provides opportunities that should not be missed for innovative developments. There is sufficient evidence already for health care purchasers to lay down a blueprint for adolescent services and the providers should 'grasp the nettle'.

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PERSONAL PRACTICE

Factitious illness: recognition and management

D M Eminson, R J Postlethwaite

Abstract

An analysis of Munchausen syndrome by proxy is proposed which involves a categorisation of parental behaviour in terms of desire to consult and ability to distinguish the child's needs from parents' own needs. The Munchausen syndrome by proxy case is proposed as one extreme of a much broader and commoner group for which the term factitious illness is used. An outline of assessment and investigation is given, applicable to all degrees of factitious illness, together with a model of collaboration between paediatrician and child psychiatrist. The role of the child psychiatrist is described. Collaboration results in a broader analysis of the situation which facilitates understanding and points the way to appropriate intervention.

(*Arch Dis Child* 1992;67:1510–6)

Munchausen syndrome by proxy has received considerable attention recently as it is recognised to take its place among other forms of child abuse.[1] The physical and emotional harm that abuse causes children has been amply demonstrated,[2] and recent work suggests significant co-morbidity in siblings of children suffering Munchausen syndrome by proxy.[3] A vast literature exists of different ways of poisoning, suffocating, or otherwise damaging children in order to produce symptoms for health care professionals to investigate and treat. This literature gives a strong sense of the horror and confusion of paediatricians who patiently pursued what they thought were 'real' symptoms, only to realise slowly that parents were 'tricking' them.

This sense of horror and fury is similar to that which adult physicians first felt when meeting patients with Munchausen's syndrome and was recognised by Asher[4] and discussed by Taylor.[5] It was met again when physical and sexual abuse of children were first recognised. We believe these emotions arise when a transaction occurs that seems to break all the unwritten rules of contact between parents or patients and physicians. Such unwritten rules are, for example, that patients (parents) are telling the truth as they see or experience it or that parents generally do their best for their children. It also happens when doctors have no framework within which to understand the behaviour they see. This paper attempts to provide a framework within which this behaviour can be categorised. It is hoped that this categorisation is a precursor of greater understanding and will lead eventually to better strategies for treatment and remediation, as has occurred with physical and, to some extent, sexual abuse.

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Cases in which parents have actively procured symptoms (that is true Munchausen syndrome by proxy) are rare. Far more common are cases where the mother has merely invented an illness story for the child without resorting to direct physical action to procure it.[3] These cases, however, will tend to be presented only with invented histories, thereby making the medical profession carry out physical investigations and arrange hospital admission and further tests. These two groups of patients with illnesses procured and invented form part of the even larger group of children who are presented with very exaggerated symptoms. All these children suffer from what we believe it is helpful to call factitious illness. This term incorporates Munchausen syndrome by proxy within a spectrum of abnormal and excessive health care seeking behaviour.[5 6] We believe this term is more explicable to clinicians and is useful in the categorisation of a wide group of patients. We suggest that it is vital to delineate the parents and children who suffer factitious illness in order to minimise the physical and psychological impact of repeated investigations.

In this paper we suggest that an understanding may be gained if the parent and child behaviour is examined under three headings. First, it is helpful to recognise that in addition to being in the hinterland of child abuse, we are studying a *behaviour*: parents' consultation with professionals. This serves to remind us that professionals' behaviour is not irrelevant (discussed further below). There are two further aspects of parents' behaviour which it is useful to examine. Consultation behaviour may be studied as part of a range of responses that parents make to symptoms in their child: this is discussed in section A and represented diagrammatically in fig 1. Finally, this behaviour may be looked at another way, in terms of parents' ability to distinguish their child's need from their own. Factors affecting parents' abilities are discussed in section B. These two categorisations are then combined in fig 2.

Section A

THE FIRST DIMENSION—APPROPRIATENESS OF PARENTS' DESIRE TO CONSULT

The range of health care seeking by parents for their children is represented in fig 1.

Professionals recognise a range of normal consultation behaviour by parents (points 4, 5, 6). Sometimes (commonly) parents and professionals are in almost complete agreement

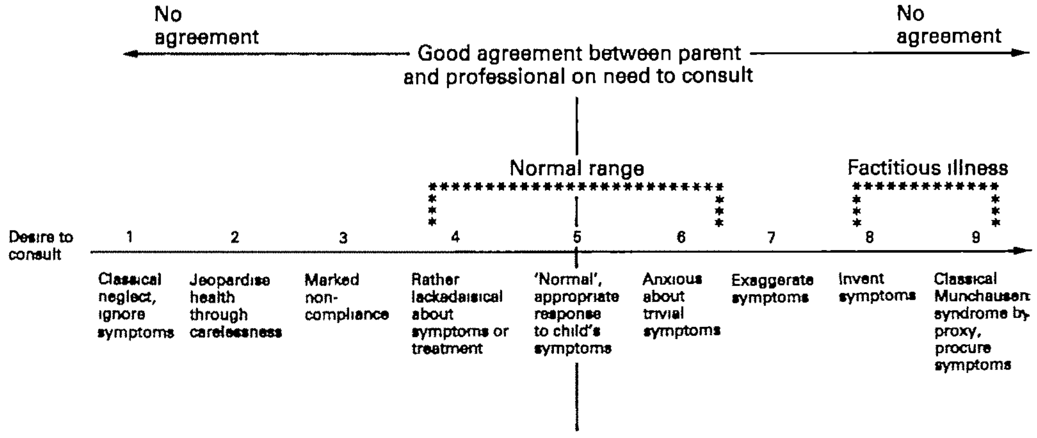
No agreement
Good agreement between parent and professional on need to consult
No agreement
Normal range
Factitious illness
Desire to consult
1
2
3
4
5
6
7
8
9
Classical neglect, ignore symptoms
Jeopardise health through carelessness
Marked non-compliance
Rather lackadaisical about symptoms or treatment
'Normal', appropriate response to child's symptoms
Anxious about trivial symptoms
Exaggerate symptoms
Invent symptoms
Classical Munchausen syndrome by proxy, procure symptoms

Figure 1 Parents' desire to consult for their child's symptoms

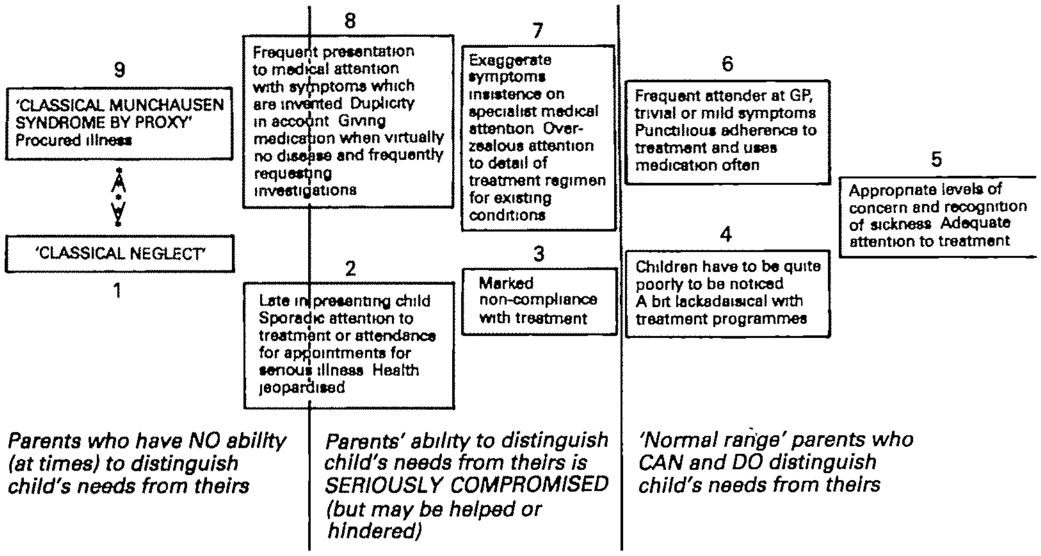
9
'CLASSICAL MUNCHAUSEN SYNDROME BY PROXY' Procured illness
'CLASSICAL NEGLECT'
1
8
Frequent presentation to medical attention with symptoms which are invented Duplicity in account Giving medication when virtually no disease and frequently requesting investigations
2
Late in presenting child Sporadic attention to treatment or attendance for appointments for serious illness Health jeopardised
7
Exaggerate symptoms insistence on specialist medical attention Over-zealous attention to detail of treatment regimen for existing conditions
3
Marked non-compliance with treatment
6
Frequent attender at GP, trivial or mild symptoms Punctilious adherence to treatment and uses medication often
4
Children have to be quite poorly to be noticed A bit lackadaisical with treatment programmes
5
Appropriate levels of concern and recognition of sickness Adequate attention to treatment
Parents who have NO ability (at times) to distinguish child's needs from theirs
Parents' ability to distinguish child's needs from theirs is SERIOUSLY COMPROMISED (but may be helped or hindered)
'Normal range' parents who CAN and DO distinguish child's needs from theirs

Figure 2 The spectrum of health care seeking by parents for their children

about the need to consult (point 5). A 'normal range' of health care seeking, however, also encompasses a group of parents who exhibit more anxiety than their doctor. This might manifest itself as frequent attendance at general practice for trivial or mild symptoms, punctilious adherence to treatment, and frequent use of medication (point 6). Another variety of normal health care seeking behaviour describes parents who are less anxious than the doctor. These parents will tend to present their children later in an illness than is ideal and are a little lackadaisical with treatment programmes (point 4).

One pole in this dimension, well outside the normal range, is characterised by a gross discrepancy between parental and professional views; this is Munchausen syndrome by proxy (point 9). In Munchausen syndrome by proxy parents seek health care where an objective professional view would suggest this is quite unnecessary. The difference between the parents' desire to consult and the objective professional view of their child's health is so huge that the parents have to procure illness, in order to force doctors to investigate and treat it.

One step back towards 'normal' are families where symptoms are invented or grossly exaggerated by the parents (point 8). These and the Munchausen syndrome by proxy groups both fall into the category of factitious illness. Between this group and normal but punctilious health care seeking behaviour (point 5) lie parents who are insistent on specialist medical attention and show over zealous or intrusive attention to detail of treatment regimens for existing conditions (point 7). These parents are distinguished from those of factitious illness by virtue of the symptoms being neither invented or grossly exaggerated, but dwelled upon and taken round many different specialists.

The other pole of the dimension concerns parents who also show a great difference in the level of concern that they show, compared with a 'professional's' view. These parents (point 1 show classical neglect of their children's health ignoring obvious ill health. Those with a slightly greater desire to consult (point 2) include a group of parents who jeopardise the health of their children because of late presentation with serious illness or sporadic attention to treatment More common again (point 3) are various forms of non-adherence with treatment regimens which shade in to the normal range' (points 4, 5, 6). It is likely that community paediatricians see more of this end of the spectrum than do hospital paediatricians, except where children have a serious chronic illness that should bring them to clinics and should receive treatment.

SECOND DIMENSION—ABILITY OF PARENTS TO DISTINGUISH THE CHILD'S NEEDS FROM THEIR OWN

In paediatrics, children are seen whose parents' behaviour is at all points of the spectrum in fig 1, but specialists are more likely to see an excess of children and parents from points 6 upwards. Though this analysis is helpful in examining the parents' desire to consult and the degree of discrepancy from the 'objective' professional view, further elucidation may be gained if the links between the two ends of the spectrum are made. This involves analysing the behaviour along the dimension of the parents' ability to distinguish the child's needs from their needs. For ease, three groups can be identified.

(a) Parents who cannot distinguish their needs from the child's and who will satisfy their own needs first (point 1, neglect and point 9, Munchausen syndrome by proxy).

(b) Parents whose ability to distinguish their child's needs is severely compromised, so that the child's needs will be heeded variably and inconsistently (points 2, 3, 7, 8).

(c) Parents who can adequately, though variably, distinguish their needs from the child's (points 4, 5, 6).

Expressed diagrammatically (fig 2), the result of applying this categorisation to the previous figure is to demonstrate the similarity between the two ends of the spectrum.

Section B

FACTORS AFFECTING THE PARENTS' PRESENTATION OF THEIR CHILDREN AT MEDICAL FACILITIES (CONSULTATION BEHAVIOUR) AND THEIR ABILITY TO DISTINGUISH THEIR CHILD'S NEEDS FROM THEIR OWN

All clinicians are aware that factors in parents are significant in affecting which children are presented to paediatricians in their clinics. Maternal mental health has been shown to affect attendance rates in outpatients.[7–9] In all situations, several other factors may affect the parent and child dyad in altering their likelihood of seeking health care in response to symptoms in the child or anxieties in the parent.

Many of the factors in parents will affect both their consultation behaviour and their ability to distinguish their child's needs. It is likely that the same factors affect *all* parents and children and result in their occupying different points on the spectrum at different times. It seems intuitively unlikely that any parent would move though *many* 'points', but this merits much further research.

Factors in the child:

(a) The child's tendency to experience somatic symptoms, and other aspects of mood and temperament (anxiety, depression, histrionic traits).

(b) The history of the child: previous or coexisting illness in that system or a serious illness earlier in the child's life.

(c) Learning that physical symptoms elicit parental attention better than other signals.

Factors in the parent:

(a) Intellectual ability: inability due to low intelligence to recognise the importance of the physical symptom in the child.

(b) Extreme youth.

(c) Social circumstances and stresses: distractions, difficulty with partner, finance, job or the parent's or family's health, bereavements.

(d) Mental health: anxiety, depression, or other psychological or psychiatric problems including psychotic illness.

(e) Early experience combined with personality and social factors. In general, the evidence suggests that having one's own needs met in childhood makes a parent more likely to be able to meet their child's needs, but individual parents' histories are not easy to analyse categorically.

These issues figure prominently in the explanations for the behaviours of the Munchausen syndrome by proxy mother.[10] Though the mechanisms and personal histories require much further study, it is evident that a group of women derive gratification from the medical and nursing attention gained when their children are in hospital or under medical investigation. Research, though anecdotal, suggests these women have a history of abusive experience in their own childhoods, have abnormal illness behaviour themselves, possess a variety of unusual personality traits, and are single or in unsupportive relationships (C N Bools, personal communication).[10] These mothers seem to adopt this pattern of behaviour as a result of a combination of inherent personality characteristics, early experiences, a later personal predicament, and the demands/availability of children as a source of vicarious satisfaction. There is a suggestion that once this pattern of behaviour has developed, it is very difficult to dislodge.

Factors in the wider family:

(a) The general tendency to somatise or to be stoical.

(b) Different cultural groups have been shown to vary in relation to frequency of presentation at clinics.

Factors in society:

(a) Factors increasing general anxiety about health, for example, a recent meningitis outbreak.

(b) Factors resulting in a decrease in presentations, for example a recent scandal such as media attention to doctors' 'reporting' of parents to social workers.

It will be obvious that all the factors interact with each other to alter the likelihood of any particular parent and child consulting for, ignoring, or inventing any symptom.

We shall now turn to the management of those children where presentation to the paediatrician suggests that a diagnosis of factitious illness may be considered; in other words, where parental concern for their children's health is very excessive, and illness may be invented or procured. It should be emphasised that this is an analysis that concentrates upon understanding parental behaviour. Children may or may not have organic illness of varying degrees of severity, whatever their parents' behaviour.

Characteristics of children presented with factitious illness

(1) The initial presentation which alerts the paediatrician is a child whose mother describes numerous physical complaints: usually more than five, often more than 10. These complaints are often presented in a confused picture including both physical and behavioural symptoms and not conforming to any easily recognisable condition.

(2) The child will be presented with symptoms which are unusual or serious, but also are either: (a) by their nature unverifiable, for example sudden pain in the penis or (b) though striking, not corroborated, for example red motions, blood in the urine.

(3) The history given by the parent is justified in an unusual way: (a) the explanations for symptoms are often bizarre or (b) after repeated discussion these explanations are tenaciously retained. In order to continue to hold to this belief supposed witnesses will be advanced in support. These 'witnesses' often have status to emphasise their reliability (friends or neighbours with medical, nursing, or paramedical training, general practitioners).

(4) The children show few if any physical signs and those found are incidental to the presenting complaints.

(5) There are extensive claims of serious illness that has been identified at other hospital(s).

(6) The patients are usually accompanied only by their mothers, rarely by their fathers. Mothers often give a history of illness themselves, usually with little detail that can be verified.

Despite the striking and extensive histories that these patients produce, the factitious origin of the symptoms frequently goes unrecognised. A number of factors contribute to this.

(1) Few patients exhibit all the features.

(2) The possibility of factitious illness is not considered, medical training tending to place emphasis on a rather narrow form of information and history gathering.

(3) The parents hide from the paediatrician the complex pattern of previous medical care. Superficially, an innocuous history of contact with other professionals is given; in a busy clinic this can easily elicit the further investigations the parents seek.

(4) A trivial positive finding or abnormal result, either on history or with investigation, can mislead the paediatrician who focuses on this. Such a focus obscures the overall picture.

(5) It is only with attention to detail and corroboration of the history that the complex picture emerges and this usually requires a number of assessments.

Assessment and management

Rarely will a firm diagnosis be established at the first assessment and factitious illness is likely to be only one of a number of more or less likely diagnoses. Several steps are necessary in the painstaking process of establishing the diagnosis, and both parents must be invited to appointments.

STAGE ONE

First, a very detailed history is required of the child's illness past and present. This would seem a routine element in any paediatric assessment but when factitious illness is considered in the differential diagnosis, the details need to be much more precise. It must be established exactly who is supposed to have seen what, when and where; both the details and parents' agreement to these details should be recorded in the notes. Despite the account being carefully agreed, contact with the 'witness' often fails to verify the story. Exactly the same precision is required in gathering the history of contact with other medical services.

Second, a detailed history of illness in siblings and parents is required. The family's current social circumstances, stresses, and supports merit inquiry.

Third, the child must be examined and the appropriate preferably non-invasive investigations performed to exclude truly likely physical explanations.

Fourth, the previous medical records of child and siblings and, where necessary, parents must be pursued and scrutinised. This is time consuming but crucial if a full picture of the family's pattern of illness and health care seeking behaviour is to be understood. It is this process that reveals the complex pattern of contact with medical services. Previous contacts might have been suppressed, unremarkable events may have been embellished by the parents, completely false stories may have been given or addresses of fictitious hospitals given. Parents may try to frustrate the search by suggesting it is fruitless, for example 'the hospital has now been burnt down', or transferred elsewhere, 'Dr X had already tried to obtain the records but they were not available'. The unwary might take these apparently helpful suggestions at face value.

Permission to seek records from other agencies should be sought.

STAGE TWO

Equipped with the detailed history and records, the clinician may now have a high level of suspicion that he or she is dealing with factitious illness. The management is still no different from any other unusual or puzzling presentation.

It is essential to see the child when the symptoms are present. It may be obvious at this visit that some significant organic disease has been overlooked in which case the child will present with the appropriate symptoms and signs.

With factitious illness, the parents show great ingenuity at evading this contact. The symptoms will occur at a time when it is judged inappropriate to attend the hospital (for example in the early morning). Problems with transport will be used as an excuse, or the child will be taken to another facility (general practitioner, another department of one's hospital, a laboratory, another hospital) with the symptoms. Many of these excuses can be forestalled by making sure the parents have transport to the hospital, a letter of introduction, and know exactly where to attend in the hospital.

Despite obsessive attention to the detail of these arrangements, with factitious illness a number of outcomes is likely. The child will not present at the hospital despite continuing symptoms because the symptoms will have been judged to have failed to reach an arbitrary threshold which the parents feel would have justified attendance at the hospital. Sometimes, often after repeated requests, the child will be presented with dramatic symptoms but no abnormal finding is identified on physical examination or with investigation.

A final possibility is that the child is not presented to the hospital with the symptom that was the focus of the previous consultation, but the excuse given at the next appointment is that a different symptom has been troublesome. (Doctor: 'He hasn't been troubled by the red motions since I last saw you, then?' Mother: 'No, but he's gone yellow . . . but you didn't tell me to bring him up if he went yellow'.)

In the course of a number of outpatient consultations, the typical mother will introduce new complaints and symptoms and will not appear reassured or enlightened by:

(a) Careful explanation that her child shows no significant ill health.

(b) Offers of benign explanations for previous symptoms.

(c) Reopening and explaining patiently the history of a previous medical contact which has shown no significant illness, but which the mother thinks has demonstrated one.

(d) Constructive refusal to carry out further investigations because the child is well.

STAGE THREE

At this point the paediatrician is under serious pressure to admit and reinvestigate the child on the grounds of vague maternal complaints, exposing the child to interruption of normal routine and schooling, painful tests, and possible risks from radiography etc. The threat is always present somewhere in the paediatrician's mind that he or she might be 'shown up' by missing a rare illness, or, that greater humiliation, an opinion will be sought from another colleague who will reveal this unusual condition. We suggest that if this aspect of medical thinking is recognised and if the possibility that the sickness might be present in the form of factitious illness has been entertained, then the paediatrician should give careful consideration to the parents' health care seeking behaviour in the dimensions outlined previously: their ability to distinguish their child's needs from theirs, and their level of concern compared with 'objective' professional appraisal. When thinking about the psychological make-up of parents reaches this level of complexity, it is suggested that the most fruitful investigation to undertake is a consultation with a child psychiatric colleague. If conversation with these colleagues suggests an assessment by the child psychiatrist should be made, this recommendation is made to the parents by the paediatrician.

The most important determinant of whether or not the parents will accept this is the conviction the paediatrician has that the consultation will be helpful. A mother who senses that the paediatrician has listened to her carefully and has her child's welfare at heart seems able to accept his assurance that referral to a child psychiatrist, which she might not particularly welcome, can be helpful. The paediatrician must convey with confidence that he is not trying to dispose of a problem, and that psychiatry is neither unnecessarily stigmatising nor unhelpful.

The role of the child psychiatrist

The training of child psychiatrists involves acquiring a combination of skills that are relevant to this situation. Initially their training is with the adult psychiatrically sick and only subsequently with children. Earlier generic medical training (often, also as junior paediatricians) equips child psychiatrists to understand and have a physician's view of organic sickness in children and adults. Subsequent postgraduate clinical work in child psychiatry involves constant assessment of interactions between parents and children, so that a vocabulary to describe relationships is readily available. As a result, the child psychiatrist can make a contribution as follows:

(1) In assessing the degree of psychological disturbance suffered by the child and forming a view of the aetiology of this and planning management.

(2) Examining the parent(s) and assessing their mental well being, personality functioning and current relationships, stresses, and supports.

(3) Examining current interactions between parents and child (and other family members where possible) and giving consideration to the likelihood of this family responding to intervention.

These assessments will be made through routine child psychiatric history taking, which involves systematic examination of the child's history, development, and family background. This includes re-examining the parent's own history in some detail with careful attention to issues (such as parental illness and illness behaviour, psychiatric illness including depression, a history of physical and sexual abuse, child rearing and relationship difficulties) that may be highly relevant to the aetiology of factitious illness. In addition, if not established earlier, the viewpoints of independent sources, such as the child's school, health visitor, and other parents and grandparents will be looked for.[11]

In summary then, the child psychiatrist presents an understanding of the child's symptoms in the context of his predicament.[12] Both the history of parent and child, the way in which it is given, and the relationships seen in the interview, will enable the child psychiatrist to present a view of the issues relating to the child's symptoms, and a view of factors affecting parental health care seeking behaviour.

Further management

On meeting after the child psychiatric assessment, paediatricians and child psychiatrists may agree the child is at serious risk of preventable physical or emotional harm where a parent is damaging the child's health through procuring sickness, or endangering it through repeated hospitalisation, investigations, and time away from normal life. The local authority may need to be consulted with a view to calling a case conference. Consulting Professor Meadow's outline of management is useful.[13]

In these very serious cases, any legal action is taken against a background of assessment of a broad range of physical and emotional capacities in child and parents. If subsequent events result in permanent separation of parent and child, professionals may have later involvement with the child if (as often occurs), he or she has had a mixture of mild physical illness with factitious illness, or because of psychological illness resulting from the emotionally abusive environment.

We have experience of several other outcomes. In the most optimistic cases the psychiatric assessment enables the mother to feel accepted and her predicament understood, perhaps in a more profound way than has happened before. If such trust develops, any necessary psychiatric treatment for parent and child may be possible using individual and family treatment approaches that will not be detailed here.[10] [14] A psychiatric social worker, play or other individual therapist may have a role. Physical complaints rarely disappear however, and close monitoring of health care seeking with regular physical examination and reassurance is necessary. The child psychiatrist's medical qualification is helpful here in allowing regular limited examination at the psychiatric appointments as well as containing anxiety between paediatric visits.

In these cases, flurries of new physical symptoms are often related to new life stresses and the family may start to recognise and acknowledge this. The pattern is described to the family and accepted by both paediatrician and psychiatrist; it is not criticised or rejected; improvement does not depend on the mother achieving insight. The general practitioner needs to understand the pattern and hold the mother's anxiety by encouraging her to phone for reassurance and not to seek new referrals. A period of several months or years of continued paediatric and psychiatric attendance (without unnecessary investigations and admissions) is usually required and continued intermittent surveillance may prevent further episodes. Junior staff need careful supervision to prevent their interrupting the treatment process with an unnecessary admission, perhaps after a call from a locum or deputising doctor who does not know the family, but not all such crises can be prevented.

In other cases, the psychiatric assessment is permitted and some greater understanding of aetiology and current dynamics is gained, but the mother cannot be engaged in treatment either on behalf of her child or herself. Sometimes she will continue to attend the paediatrician and through liaison meetings the psychiatrist may continue to have a role in ensuring and promoting the child's emotional development. Collaboration with other professionals and careful containment of new consultations is necessary, as above.

A further outcome occurs when parents depart from attendance at paediatric and psychiatric clinics simultaneously and restart the process of consultation for factitious illness through their family doctor with a new set of specialist appointments. Pointing out the pattern to the newly recruited professionals is usually fruitless, unless they have some experience of factitious illness and understanding of the dynamics of parental health care seeking and consultation behaviour.

Further work may involve setting up good communication with general practitioners, health visitors, and community services where attendance at hospital appointments is sporadic but where the risk of a new bout of seeking specialist opinions remains. The general practitioner serves as an excellent gatekeeper but may need support; health visitor and community services monitor the child's school attendance and normal physical development. A number of children have mild chronic illnesses (constipation, an occasional urinary tract infection, mild asthma) that can become the kernel of a new bout of factitious symptoms unless viewed objectively in terms of severity.

Characteristics of mothers

The mothers we have engaged in psychiatric treatment, themselves only a small percentage of those who are seen by the child psychiatrist, are a disturbed group of women in terms of parenting abilities (in the broadest sense), personality functioning, and ability to form relationships. All have had early experience that was abusive at an emotional or physical level, although on occasion this is suggested rather than actively acknowledged. Although these mothers' capacity to cope with current difficulties without presenting their child for paediatric care can be supported, their own concurrent psychiatric difficulties treated, their child helped to independence of maternal symptom production, and they themselves helped to find ways in which some personality maturation may take place, they remain highly vulnerable to using this method of meeting their own needs.[2] [3] Even so, we believe strenuous efforts to engage these families in treatment are worthwhile in terms of the quality of life for the children, even before considering the savings in unnecessary hospital stays and investigations.

The children who stay within families where factitious illness is common have not been studied extensively. Retrospective studies of adults with abnormal illness behaviour would suggest that this may be one of the outcomes.[15] The extent to which it is proper to generalise from less unusual health care seeking parents (for example parents with psychosomatic illness or anxiety) to examine the results for families with greater parental health care seeking behaviour and less ability to distinguish their child's needs is unknown.

Conclusion

We have presented a model of collaborative working in assessment and treatment of parents and children where factitious illness is considered a likely part of the differential diagnosis. We would emphasise that a known ordinary physical illness explaining *part* of the symptoms is common, and this only increases the need for collaboration because of the complexities. A two dimensional spectrum categorising parental behaviour is advanced, which requires validation clinically. Collaborative research between child psychiatrists and paediatricians will elucidate this area further. The strength of the collaboration rests on the understanding, achieved jointly, of the child's physical and emotional state, the parental capacities and their predicaments. This is in contrast to a sequential model in which referral to the child psychiatrist follows exclusion of a physical cause for symptoms and is usually a transfer of care. (Of course this sequential model may also be appropriate in straight forward cases of hysteria, or psychiatric illness presenting with physical symptoms—for example anorexia nervosa, depression presenting with abdominal pain.) It is generally accepted with recurrent symptoms in children that the dialectic of physical versus psychological be rejected in favour of more complex categorisations.[16] The pattern of paediatric and child psychiatric cooperation we have evolved to meet the extreme challenge of factitious illness in children offers a paradigm of paediatric–child psychiatric cooperation adaptable for a much larger area of paediatric practice.

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REFEREES AND STAFF

Our referees

Submitted manuscripts are initially seen by the editors or associate editors who then send them to one or two expert advisers for assessment. We thank the following people who kindly reviewed papers for our journal between September 1991 and September 1992. Their expertise and the time so generously given have been a major factor in maintaining high standards.

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Staff changes

We welcome Dr Sheila McKenzie as a new associate editor with a special interest in respiratory disease. She is a consultant paediatrician at the Queen Elizabeth Hospital for Children, London, and was previously a convenor of the respiratory group of the British Paediatric Association.

We thank Professor Brian Wharton and Dr Michael Silverman who have completed their periods of office as associate editors for their conscientious and meticulous work for the journal.

We thank the following members of the editorial committee for their invigorating contributions and sound advice to the journal: Dr M J Dillon, Dr I Hann, and Dr J W Keeling. We welcome the following as new members of the editorial committee:

Professor O Eden, oncologist at St Bartholomew's Hospital, London
Dr S Logan, senior lecturer in epidemiology at the Institute of Child Health, London

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LETTERS TO THE EDITOR

Fourteen cases of imposed upper airway obstruction

SIR,—When pointing out the difficulty with covert video surveillance for the detection of imposed upper airway obstruction, Samuels *et al* suggest that suffocation can be diagnosed by using physiological recording.[1] They say, 'the pattern considered suggestive, but not diagnostic of imposed upper airway obstruction, was regular breathing which was suddenly interrupted by the onset of large movement artefact on the breathing movement signal in combination with a pattern of obstruction—that is, continued breathing movements, absent air flow, and a gradual fall in SaO_2 [arterial oxygen saturation]'. In the abstract, they claim these are 'characteristic findings', a view now propagated in an editorial in the *Lancet*.[2]

Despite their claim, these findings cannot be considered pathognomic of suffocation. There are many natural reasons for such findings, for example, back arching, fitting, or obstructive apnoea The figure illustrating suffocation does not fulfil their own criteria Absent air flow was not confirmed. There was no tachycardia or bradycardia. The movement monitor showed increased movement but at the same rate as the normal breathing.

The following case illustrates the difficulty of interpreting data recorded during an apnoeic episode without a visual record of the event A healthy 3 day old term infant was monitored with two staff and the mother present. Heart rate, oxygen saturation waveform, oxygen saturation, chest movement, and respiratory frequency were recorded. The video recorder was not working so there was no permanent visual record The recording started normally. The baby then suddenly stiffened, arched her back and became blue. The mother picked her up and patted her back. The recording showed movement disturbance and initial tachycardia followed by bradycardia. The oxygen saturation was disturbed by movement Breathing slowly re-established spontaneously, the heart rate rose, and the oxygen saturation signal returned. As breathing became more regular, tachycardia occurred and the infant cried, again disturbing the signals and thus their interpretation.

Subsequently, it was difficult to correlate what happened with the recording. Without video recording the staff and mother were unable to distinguish the effect on the recording of the mother's action and the infant's condition. The recording of this naturally occurring episode is virtually identical to the description of Samuels *et al* 'characteristic of imposed upper airway obstruction', although of course there was no suffocation.

If the ideas of Samuels and his colleagues are accepted mothers of apnoeic babies will be under suspicion because they were alone when the baby had apnoea. The infants may be submitted to physiological recordings which could be used to 'form documentation which may be invaluable as evidence to confirm abuse'. Those working in child abuse must appreciate that physiological recordings, without simultaneous video recording showing suffocation, cannot be used to 'confirm abuse'.

If we are persuaded by this paper to accept this technique of diagnosis, innocent mothers may be accused of a serious crime from which they will find it hard to defend themselves

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1 Samuels MP, McClaughlin, Jacobson RR, Poets CF, Southall DP. Fourteen cases of imposed upper airway obstruction *Arch Dis Child* 1992;**67**:162–70
2 Anonymous Diagnosing recurrent suffocation of children. *Lancet* 1992,**340**:87

Professor Southall and Dr Samuels comment:
Morley *et al* offer no data to substantiate the opinions in their letter. They have selected out of context statements which presumably support their view that both physiological recordings during apparent life threatening events (ALTE) and features of the parental history cannot be used to identify those infants, possibly suffering imposed upper airway obstruction, who should undergo covert video surveillance (CVS). For example, the first two sentences contain conflicting statements concerning 'diagnosis'.

Without an opportunity to examine the physiological recording they propose to be identical to the pattern we find suspicious, it is clear that, by definition, their described event could never be due to imposed upper airway obstruction because two staff members were present when it began One of the most important features of physiological recordings during imposed upper airway obstruction is that the event *begins* in the presence of the perpetrator alone and does not correlate with the history given (for example, the parent might state that the infant was asleep when the recording will clearly show a pattern consistent with being active and awake)

Unfortunately imposed upper airway obstruction, as well as fabricated data (Munchausen syndrome by proxy), represent frequent mechanisms for recurrent ALTE. In a recent study (submitted for publication) ALTE in four of 109 patients presenting with recurrent episodes were due to suffocation and seven of 109 involved the fabrication of data. In addition, in a prospective study involving the confirmation by third parties of the histories given by the parents of infants with recurrent ALTE proved to be due to natural mechanisms, it *is* usual for a proportion to begin in the presence of other observers (data under collection)

We receive between one and five patients a week for the investigation of ALTE from all over the UK and have almost daily experience in the interpretation of physiological recordings during ALTE. Morley *et al* offer no such experience in their letter, in presentations, or in published papers They offer no suggestions as to how imposed upper airway obstruction should be diagnosed, if not as suggested in our paper (see abstract for summary). We do not use physiological recordings alone as evidence for this form of child abuse We use them as evidence which is objective. We combine the physiological data with all of the other clinical history, including validation of the observation of the onset of ALTE, and use this information to justify CVS. We will only go to a child protection case conference without video evidence if the latter is impossible to obtain. If CVS is prevented or fails, we will present physiological recordings to the court as evidence in context with all the other data, if there is agreement by a multidisciplinary child protection group that imposed upper airway obstruction is the probable mechanism for recurrent hypoxaemic episodes.

Our increasing experience with physiological recordings during imposed upper airway obstruction and during other 'natural' disorders causing ALTE will be published when it is ready for peer review. In the meantime, it would be much better if Morley *et al* collected data on recurrent ALTE so that they could argue convincingly with our approach In the absence of data, their 'beliefs' could inhibit paediatricians and the court from identifying this dangerous form of child abuse.

Vulvovaginitis

SIR,—I was interested in Pierce and Hart's report on this subject which provides important confirmation of the association with poor hygiene and the low incidence of urinary tract infection.[1] I was disappointed, however, not to see discussion of the use of topical oestrogen in this situation. Dewhurst in his monograph states authoritatively that 'for the majority of patients with a discharge due to low-grade bacterial infection the most satisfactory treatment is local oestrogens'.[2] I have always found this advice useful in my own practice.

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1 Pierce AM, Hart CA Vulvovaginitis. causes and management. *Arch Dis Child* 1992;67:509–12
2 Dewhurst CJ. *Practical pediatric and adolescent gynecology* New York. Marcel Dekker, 1980 87.

Dr Pierce comments·
In the series we used topical oestrogens routinely in the treatment of labial adhesions. In the early part of the study we also used it in some cases of vulvovaginitis but now rarely do so. We found that treatment of a triggering factor such as threadworms, bacterial infection or constipation, coupled with strict attention to hygiene was more effective. In addition we found that the oestrogens sometimes increased the redness and irritation, and often the vulvovaginitis recurred after the treatment was stopped This led to concerns that, in spite of instructions to the contrary, the cream would continue to be used with the danger of absorption of oestrogens

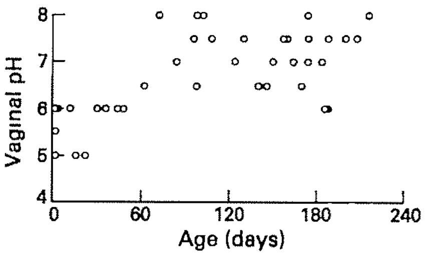
Vulvovaginitis and vaginal pH

SIR,—We read with interest the article by Pierce and Hart on vulvovaginitis[1]; there was only one patient less than 12 months of age in their 200 cases. They mentioned that the vaginal mucosa of the newborn girl is affected by maternal oestrogens, the effect of which decreases until about 6 months of age. In females of reproductive age the vaginal pH is acidic as a result of oestrogenic stimulation and the colonisation of the vagina by the lactobacillus.[2] We studied the vaginal pH in babies less than 8 months to determine if we could detect a declining oestrogen effect on the vaginal mucosa

Thirty eight babies, inpatients in the Cork Regional Hospital and St Finbarr's Hospital, were examined. Ages ranged from 2 to 216 days. The vaginal pH was measured using Multistix (Ames, Bayer Diagnostics) which have a pH range from 5–8·5. The indicators for blood, ketones, etc, were cut off, leaving the pH indicator at the tip of the strip, which was then cut lengthways into three strips. The indicator stick was gently placed in the introitus until moistened by the vaginal secretions. Secretions were scanty after the first 6 to 8 weeks and there was sometimes doubt as to whether or not there had been a colour change. In this situation the procedure was repeated, leaving the pH sticks in place for about thirty seconds. The reading was then omitted if the indicator paper was not wet.

The results of the study (figure) show that there was a distinct change in vaginal pH at about 8 weeks (about 60 days). It is possible that the pH could have been less than 5 on three occasions as this was the lower limit of the range, but the values were recorded as 5 The mean (SE) vaginal pH, under 8 weeks, was found to be significantly lower at 5·7 (0·48) than the mean pH, over 8 weeks, at 7·13 (0·32) (p<0·001).

We conclude that there is a significant change in vaginal pH at around 8 weeks of age. McKiernan has previously studied hormonal effects in babies using breast tissue as a 'bioassay'[3] His findings were at variance with the suggestion that maternal oestrogen was the only source of the oestrogen and it was likely that endogenous production of hormones may also be important. The changes in vaginal pH are chronologically different to the changes in breast development in infancy, but the endocrine basis for this difference is unclear. The relative resistance of babies to vulvovaginitis in infancy may be due to an oestrogen effect in early infancy but our study suggests that this effect does not persist beyond the first eight weeks of life.



Cross sectional study of vaginal pH in babies up to 8 months of age.

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1 Pierce AM, Hart CA, Vulvovaginitis causes and management. *Arch Dis Child* 1992;67:509–12.
2 Cruickshank R, Sharman A. The biology of the vagina in the human subject. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1934,41:190–266.
3 McKiernan J Postnatal breast development of preterm infants *Arch Dis Child* 1984,59: 1090–2.

Fever associated with teething

SIR,—I was most interested to read the attempt by Jaber *et al* to investigate the relationship between teething and fever.[1] They suggested that teething is indeed associated with a low grade fever. There may, however, be a fundamental flaw to their study. The eruption of a tooth is not a single identifiable event but rather a process that takes place over many days. The emergence of the tooth from the bone is followed by a swelling of the gum, hardening of the surface, the first vague eruptions of the tooth through the gingival mucosa, and finally the complete emergence of the tooth. How then can a parent decide when her child is 'teething'? Quite easily, the day in which he is unwell and miserable from an incidental infection!

While the author stated that eruption of the tooth was verified at hospital, the lack of definition of that eruption suggests to me that indeed it was not closely defined. It may be that if the authors were to attempt a definition of eruption, they would have difficulty, as the mother's views of that would vary considerably.

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1 Jaber L, Cohen IJ, Mor A. Fever associated with teething. *Arch Dis Child* 1992,67:233–4.

Drs Jaber and Cohen comment:

Dr Massarano can be assured that it is possible to determine when the tooth had erupted. It may be felt, seen, or even heard when a spoon or cup is used to elicit a distinct 'ping'.

This, we agree, is a continuous process. Several colleagues have written to us to report a drop in fever after the tooth erupts, and describe such cases when the gums were lanced. This does not seem to occur if other teeth are about to erupt.

The tooth may not only push its way through the gums but a process of gum reabsorption may precede the tooth. The factor responsible for this effect could be responsible for the systemic effects we have described and would cease when the tooth erupts

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